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(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Lawrenceville-Provinceline Road, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventors: **DUBOWCHIK, Gene, M.**; 65 Spring Street, Middlefield, CT 06455 (US). **HAN, Xiaojun**; 65 Ridgecrest Drive, Cheshire, CT 06410 (US). **VRUDHULA, Vivekananda, M.**; 90 Blueberry Hill Reserve, Killingworth, CT 06419 (US). **ZUEV, Dmitry**; 31 Tammy Hill Road, Wallingford, CT 06492 (US). **DASGUPTA, Bireshwar**; 215 Ridgefield Drive, Middletown, CT 06457 (US). **MICHNE, Jodi, A.**; 339 Hunting Hill Avenue, Apartement 308, Middletown, CT 06457 (US).

(74) Agent: **MAKUJINA, Shah, R.**; Bristol-Myers Squibb Company, Laurenceville-Princeton Road, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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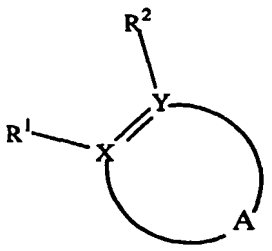
(54) Title: IMIDAZOLYL DERIVATIVES AS CORTICOTROPIN RELEASING FACTOR INHIBITORS



(I)

(57) Abstract: The present invention relates to novel heterocyclic antagonists of Formula I and pharmaceutical compositions comprising said antagonists of the coticotropin releasing factor receptor ("CRF receptor") (formula), useful for the treatment of depression, anxiety, affective disorders, feeding disorders, post-traumatic stress disorder, headache, drug addiction, inflammatory disorders, drug or alcohol withdrawal symptoms and other conditions the treatment of which can be effected by the antagonism of the CRF-1 receptor.

IMIDAZOLYL DERIVATIVES AS CORTICOTROPIN RELEASING FACTOR INHIBITORS

Field of the Invention

The present invention relates to antagonists and pharmaceutical compositions comprising said antagonists of the corticotropin releasing factor receptor ("CRF receptor") useful for the treatment of depression, anxiety, affective disorders, feeding disorders, post-traumatic stress disorder, headache, drug addiction, inflammatory disorders, drug or alcohol withdrawal symptoms and other conditions the treatment of which can be effected by the antagonism of the CRF-1 receptor.

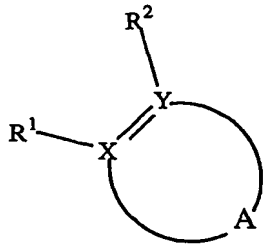
Background of the Invention

It has been shown that the neuropeptide, corticotropin releasing factor ("CRF"), acting through its binding to the CRF-1 receptor, is a primary mediator of stress- and anxiety-related physiological responses in humans and other mammals by stimulating ACTH secretion from the anterior pituitary gland. *See* A.J. Dunn, et al., Brain Res. Rev., 15: 71-100 (1990). Antagonists of the CRF-1 receptor, both peptides (J. Gulyas, et al., Proc. Natl. Acad. Sci. U.S.A., 92: 10575-10579 (1995) and small molecules (J.R. McCarthy, et al., Curr. Pharm. Design, 5: 289-315 (1999), have demonstrated the ability to ameliorate the effects of stressful stimuli in several animal models. In addition, marked elevations of CRF in cerebrospinal fluid have been detected in a large portion of individuals diagnosed with major depression and anxiety disorders, and the levels correlate with severity of the disease. *See* F. Holsboer, J. Psychiatric Res., 33: 181-214 (1999). Following antidepressant treatment, the increased CRF levels observed in depressed patients were reduced. *See* C.M. Banki, et al., Eur. Neuropsychopharmacol., 2: 107-113 (1992); *see also* Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A. Ising M, Holsboer F J Psychiatr Res 2000, 34, 171-181. CRF has also been shown to be a key mediator of several immune system functions through its effect on glucocorticoid plasma levels. *See* E.L. Webster, et al., Ann. N.Y. Acad. Sci., 840: 21-32 (1998). Recent reviews of the activity of CRF-1 antagonists include P.J. Gilligan, et al., J. Med. Chem., 43: 1641-1660 (2000) and

J.R. McCarthy, et al., Ann. Rep. Med. Chem., 34: 11-20 (1999). There appears a need to discover novel small molecule CRF antagonists in order to treat a wide variety of human disorders including depression, anxiety, bipolar disorder, and other stress-related illnesses. *See* WO 98/35967, WO 99/01454, WO 99/10350, wo 99/67247, 00/01675, WO 00/01697, WO 00/39127, WO 00/59907, WO 00/59908, EP 778277, EP 812831.

Summary of the Invention

Thus according to a first embodiment of the first aspect of the present invention are provided compounds of Formula (I)



(I)

and pharmaceutically acceptable salts and solvates thereof

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^2 is $C(D)NR^3R^4$, D'- D''$(R^3)(R^4)$ or $CH_2N\ R^3R^4$

D' is CH_2 or a bond;

D'' is C, C-OH or CH

wherein

said C is attached to R^3 by a single or double bond;

said C is attached to R^4 by a single or double bond;

provided that

C is not attached to both R^3 and R^4 by double bonds;

said CH is attached to R^3 and R^4 by single bonds;

said C of C-OH is attached to R^3 and R^4 by single bonds;

D is O or S;

R^3 and R^4 are each independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_{1-6}hydroxyalkyl, -C_{1-4}alkylene-O-C_{1-4}alkyl, -C_{1-3}alkylene-C_{1-6}thioalkyl, -C_{2-6}alkylidene-(C_{1-4}alkoxy)$_2$, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, -C_{1-6}alkylene-CN, -C_{1-6}alkylene-heterocyclo and -C_{1-6}alkylene-aryl;

wherein said aryl of said -C_{1-6}alkylene-aryl is optionally substituted with one to three of the same or different substituents selected from the group consisting of fluoro, chloro, bromo, cyano, nitro, C_{1-4}alkyl and C_{1-3}-alkoxy;

or

R^3 and R^4 together with the nitrogen to which they are attached form a five or six-membered heterocycle,

said heterocycle optionally containing one additional heteroatom selected from the group consisting of N, S and O; and

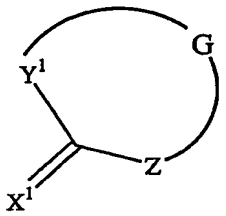
said heterocycle optionally substituted with one or more groups selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, aryl, -C_{1-4}alkylene-aryl, pyridyl and halogen;

wherein said aryl of said -C_{1-4}alkylene-aryl is optionally substituted with one to three of the same or different substituents selected from the group consisting of fluoro, chloro, bromo, cyano, nitro and C_{1-3}alkoxy;

X is C;

Y is C;

A is

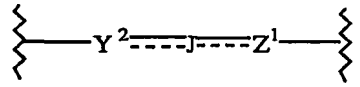


wherein

X^1 is N and is attached to X;

Y^1 is N and is attached to Y;

G is



wherein

Y^2 is N, CH, CH_2, C(O), C(S), CR^5, CHR^5 or CE^1 and is attached to Y^1;

J is CH, CH_2 , C(O), C(S), CR^6, CHR^6, a bond or CE^2;

Z^1 is CH, CH_2, C(O), C(S), CR^7, CHR^7 or CE^3 and is attached to Z;

wherein

R^5, R^6 and R^7 are each independently selected from the group consisting of -CN, -C_{1-4}-alk(en)ylene-CN, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}haloalkyl, aryl, -C_{1-4}alk(en)ylene-aryl, -C_{1-4}-

alk(en)ylene-heterocyclo, heterocyclo, -C_{1-4}alk(en)ylene- amino, -C_{1-4}alkylene-amino-C_{1-4}alkyl, aryl-amino, -amino-(C-$_{1-6}$alk(en)yl)$_{1-2}$, -amino-aryl, -amino-heterocyclo, C_{1-6}alkoxy, -O-aryl and –O-heterocyclo;

E^1 and E^2 together form moieties selected from the group consisting of C_4-alk(en)lyene, $N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N and NCHNCH;

wherein said moieties are optionally substituted with halogen, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, hydroxy, C_1-C_4alkoxy, SH, C_1-C_4thioalkyl, NH_2, $NH(C_1$-C_4alkyl) or $N(C_1$-C_4alkyl)$_2$;

E^2 and E^3 together form moieties selected from the group consisting of C_4-alk(en)lyene, $N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N and NCHNCH;

wherein said moieties are optionally substituted with halogen, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, hydroxy, C_1-C_4alkoxy, SH, C_1-C_4thioalkyl, NH_2, $NH(C_1$-C_4alkyl) or $N(C_1$-C_4alkyl)$_2$;

E^1 and E^3 together form moieties selected from the group consisting of C_4-alk(en)lyene, $N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N and NCHNCH;

wherein said moieties are optionally substituted with halogen, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, hydroxy, C_1-C_4alkoxy, SH, C_1-C_4thioalkyl, NH_2, $NH(C_1$-C_4alkyl) or $N(C_1$-C_4alkyl)$_2$;

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1$-C_4alkyl)$_2$ and CN; and

provided that

if Y^2 is N, then J is a bond and Z^1 is not CE^3;

if Y^2 is CE^1 and Z^1 is CE^3, then J is a bond ;

if Y^2 is not CE^1 and Z^1 is not CE^3, then J is not CE^2;

if J is CE^2,

then

Y^2 is CE^1 and Z^1 is not CE^3, CR^7 or CHR^7; or

Z^1 is CE^2 and Y^2 is not CE^1, CR^5 or CHR^5.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is phenyl or 3-pyridyl and is substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_1-

$_4$alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN; said substituents attached at the 2, 4 or 6-positions of said phenyl or said 3-pyridyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is 2-pyridyl and is substituted with two of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN; said substituents attached at the 3 and 5-positions of said 2-pyridyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^1 is C_{1-6}alkyl or C_{1-6}haloalkyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^1 is methyl or trifluoro methyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is $C(D)NR^3R^4$.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is $C(D)NR^3R^4$ and D is O.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is $C(D)NR^3R^4$ and D is S.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is $CH_2N\,R^3R^4$.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is D'- D''$(R^3)(R^4)$, D is a bond and D'' is C-OH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is D'- D''$(R^3)(R^4)$, D is a bond and D'' is C or CH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is D'- D''(R^3)(R^4), D is a CH_2 and D'' is C-OH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is D'- D''(R^3)(R^4), D is CH_2 and D'' is C or CH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^3 and R^4 are each independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_{1-6}hydroxyalkyl, -C_{1-4}alkylene-O-C_{1-4}alkyl, -C_{1-3}alkylene-C_{1-6}thioalkyl, -C_{2-6}alkylidene-(C_{1-4}alkoxy)$_2$, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, -C_{1-6}alkylene-CN, -C_{1-6}alkylene-heterocyclo and -C_{1-6}alkylene-aryl; wherein said aryl of said -C_{1-6}alkylene-aryl is optionally substituted with one to three of the same or different substituents selected from the group consisting of fluoro, chloro, bromo, cyano, nitro, C_{1-4}alkyl and C_{1-3}alkoxy.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^3 and R^4 are each independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_{1-6}hydroxyalkyl, -C_{1-4}alkylene-O-C_{1-4}alkyl, -C_{1-3}alkylene-C_{1-6}thioalkyl, -C_{2-6}alkylidene-(C_{1-4}alkoxy)$_2$, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{3-6}alkynyl and -C_{1-6}alkylene-CN.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^3 and R^4 together with the nitrogen to which they are attached form a five or six-membered heterocycle, said heterocycle optionally containing one additional heteroatom selected from the group consisting of N, S and O; and said heterocycle optionally substituted with one or more groups selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, aryl, -C_{1-4}alkylene-aryl, pyridyl and halogen; wherein said aryl of said -C_{1-4}alkylene-aryl is optionally substituted with one to three of the same or different substituents selected from the group consisting of fluoro, chloro, bromo, cyano, nitro and C_{1-3}alkoxy.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first

aspect wherein R^3 and R^4 together with the nitrogen to which they are attached form a five or six-membered heterocycle, said heterocycle optionally containing one additional heteroatom selected from the group consisting of N, S and O.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^3 and R^4 together with the nitrogen to which they are attached form a five or six-membered heterocycle.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein J is a bond .

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1 and Z^1 is CE^3 .

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1 and Z^1 is CE^3.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein J is CE^2.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is substituted 3-pyridyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is substituted phenyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is 2, 4, 6-trimethylphenyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein V is 2,4-dichlorophenyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^5, R^6 and R^7 are each independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, benzyl, phenyl, C_{1-3}alkyl-imidazolyl, C_{1-3}alkyl-indolyl and C_{1-3}alkyl-pyridyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH_2, J is a bond and Z^1 is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH, J is a bond and Z^1 is CH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CR^5, J is a bond and Z^1 is CH wherein said R^5 is halo.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH, J is a bond and Z^1 is CR^7 wherein said R^7 is halo.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH, J is a bond and Z^1 is CR^7 wherein said R^7 is halo, cyano or C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is C(O), J is a bond and Z^1 is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH_2, J is a bond and Z^1 is C(O).

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CH_2, J is a bond , Z^1 is CH_2, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $C(O)NR^3R^4$, R^3 is

propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CH_2, J is a bond , Z^1 is CH_2, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CH_2, J is a bond , Z^1 is CH_2, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CH_2, J is a bond , Z^1 is CH_2, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein Y^2 is CH_2, J is CH_2 and Z^1 is CH_2.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is CN or CF_3 and Y^2 is CH_2, J is CH_2 and Z^1 is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is C(O), J is CH and Z^1 is CH.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CH , J is CH and Z^1 is C(O).

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is C(O), J is CE^2 and Z^1 is CE^3 wherein E^2 and E^3 together form C_4-alk(en)lyene optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1, J is CE^2 and Z^1 is C(O) wherein E^1 and E^2 together form C_4-alk(en)lyene optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is C(O), J is CE^2 and Z^1 is CE^3 wherein E^2 and E^3 together form

$N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N or NCHNCH optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1, J is CE^2 and Z^1 is C(O) wherein E^1 and E^2 together form $N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N or NCHNCH optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1, J is a bond , Z^1 is CE^3 wherein E^1 and E^3 together form C_4-alk(en)lyene optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1, J is a bond , Z^1 is CE^3 wherein E^1 and E^3 together form $N(CH)_3$ optionally substituted with halogen, methoxy, methyl or nitrile.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein R^2 is $CH_2NR^3R^4$, R^3 is ethyl or propyl, R^4 is $-(CH_2)_2$-phenyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3 wherein E^1 and E^3 together form $N(CH)_3$ optionally substituted with halogen, methoxy, methyl or nitrile.

According to another embodiment of the first aspect of the present invention are provided compounds of Formula (I) according to the first embodiment of the first aspect wherein Y^2 is CE^1, J is a bond , Z^1 is CE^3 wherein E^1 and E^3 together form $N(CH)_3$, $CHN(CH)_2$, $N(CH)_2N$, N=NCH=N or NCHNCH optionally substituted with halogen.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=C(F)CH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is trifluoromethyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4-dichloro-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $C(O)NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=C(F)CH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=C(F)CH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is methyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is trifluoromethyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3,

E^1 and E^3 together form –CH=CHCH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein R^1 is ethyl, R^2 is $CH_2NR^3R^4$, R^3 is propyl, R^4 is $-CH_2$-cyclopropyl, Y^2 is CE^1, J is a bond , Z^1 is CE^3, E^1 and E^3 together form –CH=C(F)CH=CH-, Z is N-V and V is 2,4,6-trimethyl-phenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein "aryl" or "ar-" is phenyl or napthalenyl.

According to another embodiment of the first aspect of the present invention is provided a compound of Formula (I) wherein "heterocyclic" or "heterocyclo" is furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl, azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl or tetrahydropyranyl.

According to another embodiment of the first aspect of the present invention are compounds of Formula (I) and salts or solvates thereof selected from the group consisting of 2-methyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, 2-ethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, 5-fluoro-2-methyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, 2-methyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, 2-ethyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, 2-trifluoromethyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, 8-(2,4-dichlorophenyl)-2-methyl-8*H*-1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, 2-ethyl-5-fluoro-8-(2,4,6-trimethylphenyl)-8*H*-

1,3a,8-triaza-cyclopenta[*a*]indene-3-carboxylic acid cyclopropylmethyl-propyl-amide, cyclopropylmethyl-[5-fluoro-2-methyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl]-propyl-amine, cyclopropylmethyl-[2-methyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl]-propyl-amine, cyclopropylmethyl-[2-ethyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl]-propyl-amine, cyclopropylmethyl-propyl-(2-trifluoromethyl-8-(2,4,6-trimethylphenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl)-amine and cyclopropylmethyl-[2-ethyl-5-fluoro-8-(2,4,6-trimethyl-phenyl)-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl]-propyl-amine.

According to another embodiment of the first aspect of the present invention are compounds of Formula (I) and salts or solvates thereof selected from the group consisting of Cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine,

Cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethylphenyl-8*H*-1,3a,8-triaza-cyclopenta[*a*]inden-3-ylmethyl]-amine,

Ethyl-[2-methyl-8-(2,4,6-trimethyl-phenyl)-8*H*-1,3a,7,8-tetraaza-cyclopenta[α]inden-3-ylmethyl]-phenethyl-amine,

Cyclobutylmethyl-[2-methyl-8-(2,4,6-trimethyl-phenyl)-8*H*-1,3a,7,8-tetraaza-cyclopenta[α]inden-3-ylmethyl]-propyl-amine,

[8-(2-Chloro-4,6-dimethyl-phenyl)-2-methyl-8H-1,3a,7,8-tetraaza-cyclopenta[a]inden-3-ylmethyl]-phenethyl-propyl-amine,

[8-(2-Chloro-4,6-dimethyl-phenyl)-2-methyl-8*H*-1,3a,7,8-tetraaza-cyclopenta[α]inden-3-ylmethyl]-cyclobutylmethyl-propyl-amine,

[8-(2-Chloro-4,6-dimethyl-phenyl)-2-methyl-8H-1,3a,7,8-tetraaza-cyclopenta[a]inden-3-ylmethyl]-ethyl-phenethyl-amine,

8-(2-Chloro-4,6-dimethyl-phenyl)-2-methyl-3-(3-phenyl-pyrrolidin-1-ylmethyl)-8*H*-1,3a,7,8-tetraaza-cyclopenta[α]indene,

6-Chloro-2-ethyl-7-(2,4-dichlorophenyl)-7H-imidazo[1,2-a]imidazole-3-carboxylic acid N,N-dipropylamide,

3-[(N,N-Dipropylamino)methyl]-6-chloro-2-ethyl-7-(2,4-diclorophenyl)-7H-imidazo[1,2-a]imidazole,

6-Chloro-2-ethyl-7-(2,4,6-trimethylphenyl)-7H-imidazo[1,2-a]imidazole-3-carboxylic acid N-cyclopropylmethyl-N-ethylamide,

3-[(N-Cyclopropylmethyl-N-ethylamino)methyl]-6-chloro-2-ethyl-7-(2,4,6-trimethylphenyl)-7H-imidazo[1,2-a]imidazole,

6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amine,

6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-cyclopropylmethyl-(2,2,3,3,3-pentafluoro-propyl)-amine,

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-cyclopropylmethyl-ethyl-amine,

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-cyclobutylmethyl-(2,2,2-trifluoro-ethyl)-amine,

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-propyl-(3,3,3-trifluoro-propyl)-amine,

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-ethyl-phenethyl-amine,

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-(2-cyclopropyl-ethyl)-(3,3,3-trifluoro-propyl)-amine, and

[6-Chloro-2-trifluoromethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-imidazo[1,2-a]imidazol-3-ylmethyl]-(2-cyclopropyl-ethyl)-(2,2,2-trifluoro-ethyl)-amine.

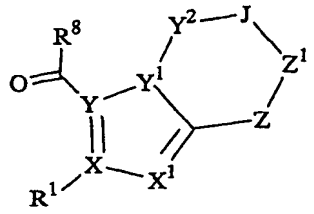
According to various embodiments of a second aspect of the present invention are provided pharmaceutical compositions comprising compounds of Formula (I) as defined herein.

According to various embodiments of a second aspect of the present invention are provided methods of treating depression, anxiety, affective disorders, post-traumatic stress disorder, post-operative stress, headache, drug addiction, eating disorders and obesity, sudden death due to cardiac disorders, iritable bowel syndrome, hypertension, syndrome X, inflammatory disorders, stress-induced immune suppression, infertility, stress-induced insomnia and other sleep disorders, seizures, epilepsy, stroke and cerebral ischemia, traumatic brain injury, yet other disorders requiring neuroprotection, drug or alcohol withdrawal symptoms, other disorders including tachycardia, congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, ulcers, diarrhea, post-operative ileus and yet other

conditions the treatment of which can be effected by the antagonism of the CRF-1 receptor by the administration of pharmaceutical compositions comprising compounds of the present invention as described herein.

According to a first embodiment of a third aspect of the present invention are provided compounds of

Formula (WHH)



(WHH)

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

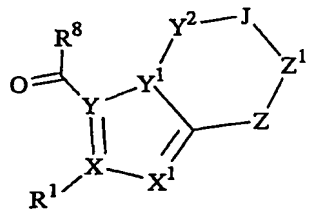
Y^2 is CH_2;

J is CH_2 or a bond;

Z^1 is CH_2 or C(O); and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN.

According to another embodiment of a third aspect of the present invention are provided processes for preparing compounds of Formula (WHH)



(WHH)

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

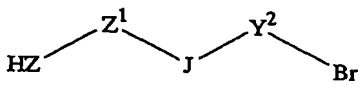
Y^2 is CH_2;

J is CH_2 or a bond;

Z^1 is CH_2 or C(O); and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN;

comprising reacting a compound of Formula (UFF)

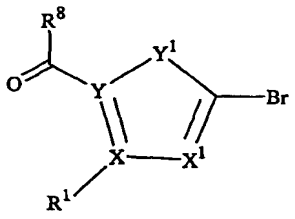


(UFF)

wherein

Z, Z^1, J and Y^2 are defined as for Formula (WHH);

with a compound of Formula (UFF ')

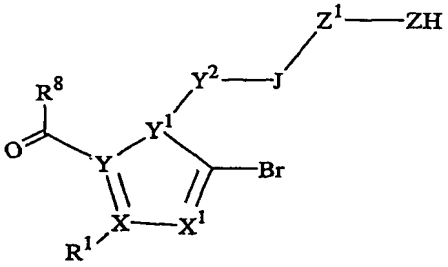


(UFF ')

wherein

R^1, R^8, X, Y, X^1 and Y^1 are defined as for Formula (WHH);

in the presence of a suitable base and polar aprotic solvent to yield a compound of Formula (VGG)



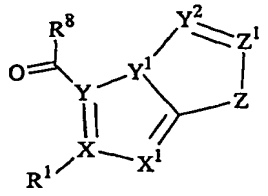
(VGG)

wherein

R^1, R^8, X, Y, X^1, Y^1, Y^2, J, Z^1 and Z are defined as for Formula (WHH);

and reacting said compound of Formula (VGG) with a high-boiling point polar aprotic solvent and a suitable silver salt under suitably high temperature.

According to another embodiment of a third aspect of the present invention are provided compounds of Formula (Z')



(Z')

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

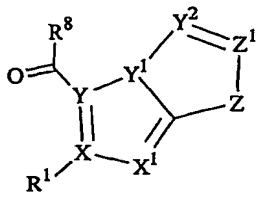
Y^2 is CH or CR^5;

R^5 is selected from the group consisting of -CN, -C_{1-4}-alk(en)ylene-CN, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}haloalkyl, aryl, -C_{1-4}alk(en)ylene-aryl, -C_{1-4}alk(en)ylene-heterocyclo, heterocyclo, -C_{1-4}alk(en)ylene- amino, -C_{1-4}alkylene-amino-C_{1-4}alkyl, aryl-amino, -amino-$(C_{1-6}$alk(en)yl$)_{1-2}$, -amino-aryl, -amino-heterocyclo, C_{1-6}alkoxy, -O-aryl and –O-heterocyclo;

Z^1 is C(O); and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1$-C_4alkyl$)_2$ and CN.

According to another embodiment of a third aspect of the present invention are provided processes for preparing compounds of Formula (Z')



(Z')

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

Y^2 is CH or CR^5;

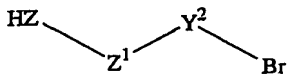
R^5 is selected from the group consisting of -CN, -C_{1-4}-alk(en)ylene-CN, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}haloalkyl, aryl, -C_{1-4}alk(en)ylene-aryl, -C_{1-4}alk(en)ylene-heterocyclo, heterocyclo, -C_{1-4}alk(en)ylene- amino, -C_{1-4}alkylene-amino-C_{1-4}alkyl, aryl-amino, -amino-(C_{1-6}alk(en)yl)$_{1-2}$, -amino-aryl, -amino-heterocyclo, C_{1-6}alkoxy, -O-aryl and –O-heterocyclo;

Z^1 is C(O); and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from

the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN;

comprising reacting a compound of Formula (X')

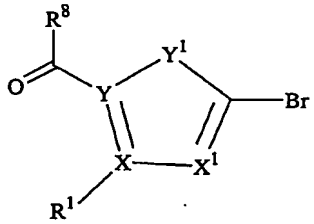


(X')

wherein

Z, Z^1 and Y^2 are defined as for Formula (Z');

with a compound of Formula (UFF ')

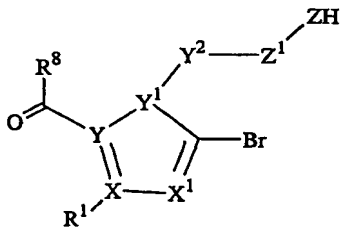


(X")

wherein

R^1, R^8 , X, Y, X^1 and Y^1 are defined as for Formula (Z');

in the presence of a suitable base and polar aprotic solvent to yield a compound of Formula (Y')



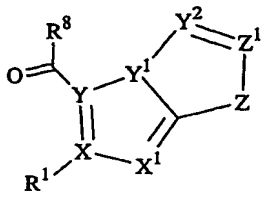
(Y')

wherein

R^1, R^8 , X, Y, X^1, Y^1, Y^2, Z^1 and Z are defined as for Formula (Z');

and reacting said compound of Formula (Y') with a high-boiling point polar aprotic solvent and a suitable silver salt under suitably high temperature.

According to another embodiment of a third aspect of the present invention are provided compounds of Formula (AA')



(AA')

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

Y^2 is CH or CR^5;

R^5 is selected from the group consisting of -CN, -C_{1-4}-alk(en)ylene-CN, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}haloalkyl, aryl, -C_{1-4}alk(en)ylene-aryl, -C_{1-4}alk(en)ylene-heterocyclo, heterocyclo, -C_{1-4}alk(en)ylene- amino, -C_{1-4}alkylene-amino-C_{1-4}alkyl, aryl-amino, -amino-$(C_{1-6}$alk(en)yl$)_{1-2}$, -amino-aryl, -amino-heterocyclo, C_{1-6}alkoxy, -O-aryl and –O-heterocyclo;

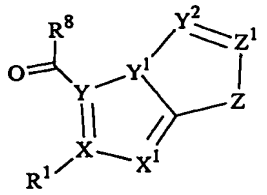
Z^1 is CR^7;

wherein R^7 is chloro or bromo; and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from

the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN.

According to another embodiment of a third aspect of the present invention are provided processes for preparing compounds of Formula (AA')



(AA')

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}thioalkyl, cyano, halo, C_{3-7}cycloalkyl, -C_{1-6}alkylene-C_{3-7}cycloalkyl, C_{2-6}alkenyl or C_{3-6}alkynyl;

R^8 is O-C_{1-4}alkyl, -$N(CH_3)(OCH_3)$ or other suitable leaving group;

X is C;

Y is C;

X^1 is N;

Y^1 is N;

Y^2 is CH or CR^5;

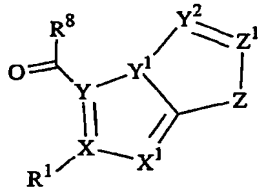
R^5 is selected from the group consisting of -CN, -C_{1-4}alk(en)ylene-CN, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}haloalkyl, aryl, -C_{1-4}alk(en)ylene-aryl, -C_{1-4}alk(en)ylene-heterocyclo, heterocyclo, -C_{1-4}alk(en)ylene- amino, -C_{1-4}alkylene-amino-C_{1-4}alkyl, aryl-amino, -amino-$(C_{1-6}alk(en)yl)_{1-2}$, -amino-aryl, -amino-heterocyclo, C_{1-6}alkoxy, -O-aryl and –O-heterocyclo;

Z^1 is CR^7;

wherein R^7 is chloro or bromo; and

Z is N-V, wherein V is phenyl, 2-pyridyl or 3-pyridyl substituted with two to three of the same or different substitutents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-6}thioalkyl, C_{1-4}haloalkyl, halogen, $N(C_1-C_4alkyl)_2$ and CN;

comprising reacting a compound of Formula (Z')



(Z')

wherein

R^1, R^8 , X, Y, X^1, Y^1, Y^2, and Z are defined as for Formula (AA'); and

Z^1 is C(O);

with phosphoryl trichloride or phosphoryl tribromide, neat or with a suitable solvent and without a base or with a suitable base.

Other embodiments of the present invention may comprise a suitable combination of two or more of the embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the invention will be apparent according to the description provided below.

Detailed Description of the Invention

The description of the invention herein should be construed in congruity with the laws and principals of chemical bonding. An embodiment or aspect which depends from another embodiment or aspect, will describe only the variables having values and provisos that differ from the embodiment or aspect from which it depends.

As used herein, "aryl" or "ar-" includes phenyl or napthalenyl.

As used herein, "heterocyclic" or "heterocyclo" includes both heteroaryl and heteroalicyclic. "Heteroaryl" includes but is not limited to furyl, thienyl,

benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl or pyrazinyl.

"Heteroalicyclic" includes but is not limited to azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl or tetrahydropyranyl. "Heteroalicyclic" further includes moieties otherwise heteroaromatic but for the addition of one or more hydrogen atoms, *e.g.*, dihydropyridine.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo and iodo and further means one or more of the same or different halogens may be substituted on a respective moiety.

Unless specificied otherwise, alkyl, alkenyl and alkynyl may be branched or straight chained. As used herein, "alk(en)yl" or "alk(en)ylene" includes alkyl or alkenyl groups. Alkenyl and alkynyl groups may contain one or more double or triple bonds respectively. Where a range of carbon atoms is designated, *e.g.*, C_{1-4}alk(en)ylene, alkenyl groups it is understood that according to the principals of chemical bonding must have at least two carbons in length.

It is to be understood that the present invention may include any and all possible stereoisomers, geometric isomers, diastereoisomers, enantiomers, anomers and optical isomers, unless a particular description specifies otherwise.

The compounds of this invention may exist in the form of pharmaceutically acceptable salts. Such salts may include addition salts with inorganic acids such as, for example, hydrochloric acid and sulfuric acid, and with organic acids such as, for example, acetic acid, citric acid, methanesulfonic acid, toluenesulfonic acid, tartaric acid and maleic acid. Further, in case the compounds of this invention contain an acidic group, the acidic group may exist in the form of alkali metal salts such as, for example, a potassium salt and a sodium salt; alkaline earth metal salts such as, for example, a magnesium salt and a calcium salt; and salts with organic bases such as a triethylammonium salt and an arginine salt. The compounds of the present invention may be hydrated or non-hydrated.

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release

formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of this invention may also be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, all using dosage forms well known to those skilled in the pharmaceutical arts. The compounds can be administered alone, but generally will be administered with a pharmaceutical carrier selected upon the basis of the chosen route of administration and standard pharmaceutical practice. Compounds of this invention can also be administered in intranasal form by topical use of suitable intranasal vehicles, or by transdermal routes, using transdermal skin patches. When compounds of this invention are administered transdermally the dosage will be continuous throughout the dosage regimen.

Compounds of the present invention may be used for the treatment of a variety of conditions including depression, anxiety, affective disorders, eating disorders and obesity (*see* Peripheral administration of CRF and urocortin: effects on food intake and the HPA axis in the marsupial Sminthopsis crassicaudata. Hope, P. J.; Turnbull, H.; Farr, S.; Morley, J. E.; Rice, K. C.; Chrousos, G. P.; Torpy, D. J.; Wittert, G. A. Department of Medicine, University of Adelaide, Royal Adelaide Hospital, South Australia, Australia. Peptides (N. Y.) (2000), 21(5), 669-677), sudden death due to cardiac disorders (*see* Use of corticotropin releasing factor (CRF) antagonists to prevent sudden death. Fossa, Anthony Andrea. (Pfizer Products Inc., USA). Eur. Pat. Appl. (2000), EP 1040831 A2), post-traumatic stress disorder, headache, post-operative stress (*see* WO 0158489 A1), drug addiction, iritable bowel syndrome (*see* Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. Tache Y; Martinez V; Million M; Wang L CURE: Digestive Diseases Research Center, Department of Veterans Affairs Greater Los Angeles Healthcare System, Bldg. 115, Rm. 203, 11301 Wilshire Blvd., Los Angeles, CA 90073, USA. AMERICAN JOURNAL OF PHYSIOLOGY. GASTROINTESTINAL AND LIVER PHYSIOLOGY (2001 Feb), 280(2), G173-7; Role of CRF receptor 1 in central CRF-induced stimulation of colonic propulsion in rats. Martinez, V.; Tache, Y. Digestive Disease Division and Brain Research Institute, Department of Medicine, CURE: Digestive Diseases Research Center, Veterans Administration Greater Los Angeles Healthcare System, University of California at Los Angeles, Los Angeles,

CA, USA. Brain Res. (2001), 893(1,2), 29-35; and Peripheral corticotropin-releasing factor and stress-stimulated colonic motor activity involve type 1 receptor in rats. Maillot, Celine; Million, Mulugeta; Wei, Jen Yu; Gauthier, Ariane; Tache, Yvette. Digestive Diseases Research Center, VA Greater Los Angeles Healthcare System, Department of Medicine, Division of Digestive Diseases, and Brain Research Institute, University of California School of Medicine, Los Angeles, CA, USA. Gastroenterology (2000), 119(6), 1569-1579), hypertension (*see* Combinations of CRF antagonists and renin-angiotensin system inhibitors. Fossa, Anthony Andrea. (Pfizer Products Inc., USA). Eur. Pat. Appl. (2000), 21 pp. and Antalarmin blockade of corticotropin releasing hormone-induced hypertension in rats. Briscoe, R. J.; Cabrera, C. L.; Baird, T. J.; Rice, K. C.; Woods, J. H. Department of Pharmacology, University of Michigan, Ann Arbor, MI, USA. Brain Res. (2000), 881(2), 204-207), syndrome X (also known as metabolic syndrome, plurimetabolic syndrome or insulin resistance syndrome) (see EP1 097 709 A2), inflammatory disorders and stress-induced immune suppression (*see* Stress, corticotropin-releasing hormone, glucocorticoids, and the immune/inflammatory response: acute and chronic effects. Elenkov, Ilia J.; Webster, Elizabeth L.; Torpy, David J.; Chrousos, George P. Pediatric Endocrinology Section, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, and Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA. Ann. N. Y. Acad. Sci. (1999), 876(Neuroendocrine Immune Basis of the Rheumatic Diseases), 1-13; Corticotropin-releasing hormone and inflammation. Webster, Elizabeth L.; Torpy, David J.; Elenkov, Ilia J.; Chrousos, George P. Pediatric Endocrinology Section, Developmental Endocrinology Branch, National Institute of Child Health and Development, National Institutes of Health, Bethesda, MD, USA. Ann. N. Y. Acad. Sci. (1998), 840(Neuroimmunomodulation), 21-32; and Peripheral corticotropin-releasing factor mediates the elevation of plasma IL-6 by immobilization stress in rats. Ando T; Rivier J; Yanaihara H; Arimura A United States-Japan Biomedical Research Laboratories, Tulane University Hebert Center, Belle Chasse, Louisiana 70037-3001, USA AMERICAN JOURNAL OF PHYSIOLOGY (1998 Nov), 275(5 Pt 2), R1461-7), infertility (*see* Corticotropin-

releasing factor (CRF) and stress-related reproductive failure: The brain as a state of the art or the ovary as a novel clue? Nappi, R. E.; Rivest, S. CHUL Research Center, Laval University, PQ, Can. J. Endocrinol. Invest. (1995), 18(11), 872-80)), stress-induced insomnia and other sleep disorders (*see* Use of CRF antagonists and related compositions for modifying circadian rhythm and treatment of depression and other conditions. Chen, Yuhpyng Liang. (Pfizer Products Inc., USA). Eur. Pat. Appl. (2001), 29 pp EP 1082960 A2; Middle-Aged Men Show Higher Sensitivity of Sleep to the Arousing Effects of Corticotropin-Releasing Hormone Than Young Men: Clinical Implications. Vgontzas AN, Bixler EO, Wittman AM, Zachman K, Lin HM, Vela-Bueno A, Kales A, Chrousos GP. Sleep Research and Treatment Center, Department of Psychiatry and Department of Health Evaluation Sciences (H.-M.L.), Pennsylvania State University, Hershey, Pennsylvania 17033. J. Clin. Endocrinol. Metab. (2001), 86 (4): 1489-1495; IL-1 is a mediator of increases in slow-wave sleep induced by CRH receptor blockade. Chang, Fang-Chia; Opp, Mark R. Neuroscience Graduate Program, University of Texas Medical Branch, Galveston, TX, USA. Am. J. Physiol. (2000), 279(3, Pt. 2), R793-R802; Blockade of corticotropin-releasing hormone receptors reduces spontaneous waking in the rat. Chang, Fang-Chia; Opp, Mark R. Neuroscience Graduate Program, University of Texas Medical Branch, Galveston, TX, USA. Am. J. Physiol. (1998), 275(3, Pt. 2), R793-R802; Non-peptidic corticotropin-releasing hormone receptor type 1 antagonist reverses restraint stress-induced shortening of sodium pentobarbital-induced sleeping time of rats: evidence that an increase in arousal induced by stress is mediated through CRH receptor type 1. Arai, Keiko; Ohata, Hisayuki; Shibasaki, Tamotsu. Department of Physiology, Nippon Medical School, Tokyo, Japan. Neurosci. Lett. (1998), 255(2), 103-106; Rat strain differences suggest a role for corticotropin-releasing hormone in modulating sleep. Opp, Mark R. Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston, TX, USA. Physiol. Behav. (1997), Volume Date 1998, 63(1), 67-74), seizures (*see* The effect of 'Astressin', a novel antagonist of corticotropin releasing hormone (CRH), on CRH-induced seizures in the infant rat: comparison with two other antagonists. Baram T Z; Koutsoukos Y; Schultz L; Rivier J Department of Pediatrics, University of California, Irvine 92717, USA MOLECULAR PSYCHIATRY (1996 Jul), 1(3), 223-6; and Astressin, a novel and

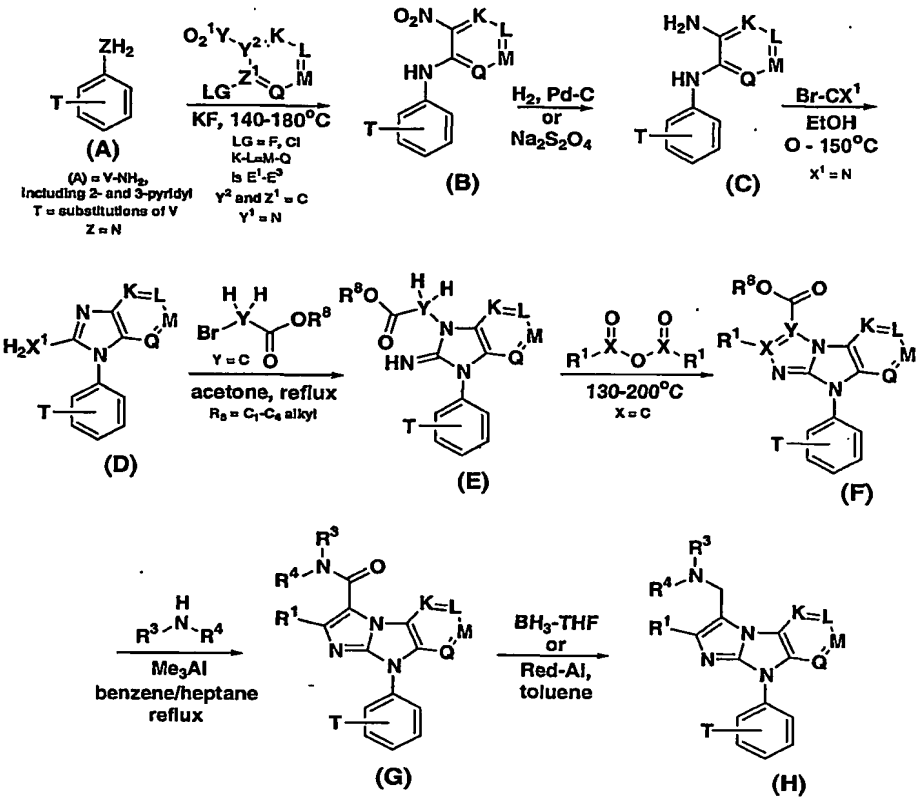
potent CRF antagonist, is neuroprotective in the hippocampus when administered after a seizure. Maecker H; Desai A; Dash R; Rivier J; Vale W; Sapolsky R Department of Biological Sciences, Stanford University, CA 94305, USA BRAIN RESEARCH (1997 Jan 2), 744(1), 166-70), epilepsy (*see* Infantile spasms. Hypothesis-driven therapy and pilot human infant experiments using corticotropin-releasing hormone receptor antagonists. Baram, Tallie Z.; Mitchell, Wendy G.; Brunson, Kristen; Haden, Elizabeth. Department Anatomy/Neurobiology, Univ. California Irvine, Irvine, CA, USA. Dev. Neurosci. (Basel) (1999), 21(3-5), 281-289; and The pro-convulsant actions of corticotropin-releasing hormone in the hippocampus of infant rats. Hollrigel, G. S.; Chen, K.; Baram, T. Z.; Soltesz, I. Department of Anatomy and Neurobiology, University of California, Irvine, CA, USA. Neuroscience (Oxford) (1998), 84(1), 71-79), stroke and cerebral ischemia (*see* Neuroprotection by corticotropin releasing factor during hypoxia in rat brain. Fox M W; Anderson R E; Meyer F B Department of Neurosurgery, Mayo Clinic, Rochester, MN 55905. STROKE (1993 Jul), 24(7), 1072-5; discussion 1075-6; Neuroprotective effects of corticotropin-releasing factor receptor antagonists. Loddick, S. A.; Chalmers, D. T.; Yatsushiro, K.; McCulloch, J.; Foster, A. C.; Rothwell, N. J.; De Souza, E. B. Neurocrine Biosciences, Inc., San Diego, CA, USA. Editor(s): Krieglstein, Josef. Pharmacol. Cereb. Ischemia 1998, [Int. Symp.], 7th (1999), Meeting Date 1998, 371-378. Publisher: Medpharm Scientific Publishers, Stuttgart, Germany CODEN: 68OZA5 Conference; Corticotropin releasing factor antagonist reduces ischemic hippocampal neuronal injury. Lyons, Mark K.; Anderson, Robert E.; Meyer, Fredric B. Mayo Clin., Mayo Grad. Sch. Med., Rochester, MN, USA. Brain Res. (1991), 545(1-2), 339-42; Focal cerebral ischemia induces CRH mRNA in rat cerebral cortex and amygdala. Wong M L; Loddick S A; Bongiorno P B; Gold P W; Rothwell N J; Licinio J Clinical Neuroendocrinology Branch, NIMH, NIH, Bethesda, Maryland 20892-1284, USA NEUROREPORT (1995 Sep 11), 6(13), 1785-8;) traumatic brain injury (*see* Evidence for the involvement of corticotrophin-releasing hormone in the pathogenesis of traumatic brain injury. Roe S Y; McGowan E M; Rothwell N J School of Biological Sciences, University of Manchester, UK EUROPEAN JOURNAL OF NEUROSCIENCE (1998 Feb), 10(2), 553-9; The effects of human corticotrophin releasing factor on motor and cognitive deficits after impact

acceleration injury. Beaumont, Andrew; Marmarou, Christina; Marmarou, Anthony. Division of Neurosurgery, Department of Physiology, Medical College of Virginia, Richmond, VA, USA. Neurol. Res. (2000), 22(7), 665-673) and yet other disorders requiring neuroprotection, drug or alcohol withdrawal symptoms, other disorders including tachycardia, congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, ulcer, diarrhea and post-operative ileus (*see* New uses for heterocyclic corticotropin-releasing factor (CRF) antagonists in treating cardiovascular diseases, osteoporosis, ulcers, and other disorders. Chen, Yuhpyng Liang; Fossa, Anthony Andrea. (Pfizer Inc., USA). Eur. Pat. Appl. (1997), 15 pp. EP 773023 A1) and yet other conditions the treatment of which can be effected by the antagonism of the CRF-1 receptor by the administration of pharmaceutical compositions comprising compounds of the present invention as described herein.

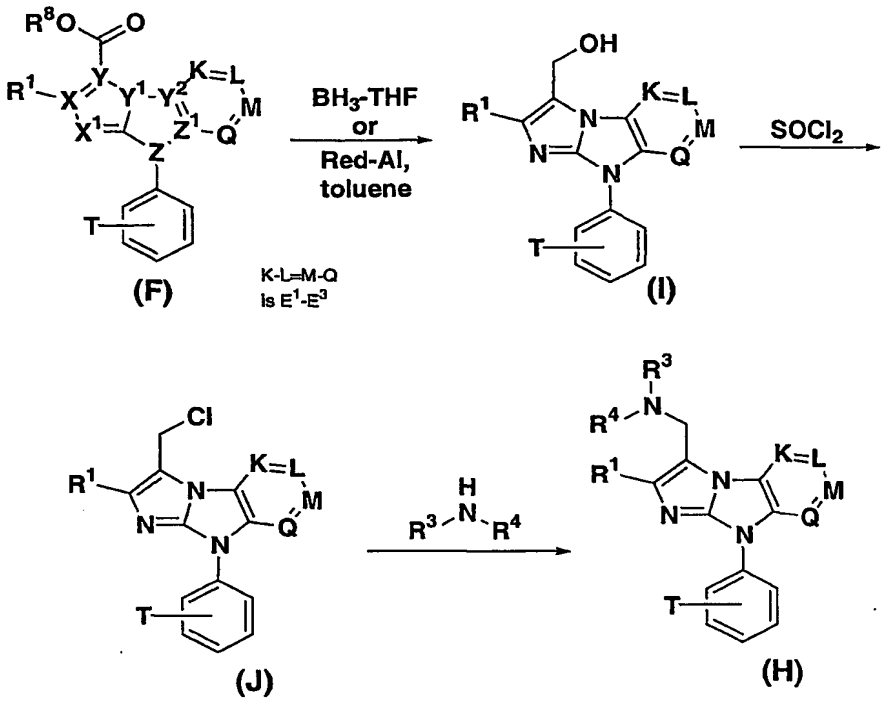
The dosage and dosage regimen and scheduling of a compounds of the present invention must in each case be carefully adjusted, utilizing sound professional judgment and considering the age, weight and condition of the recipient, the route of administration and the nature and extent of the disease condition. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level which will produce effective beneficial effects without causing any harmful or untoward side effects.

Compounds of the present invention may be synthesized according to the general schemes provided below. Variables corresponding to compounds of Formula (I) have been introduced in the schemes below at particular instances to further depict how said compounds may be synthesized. Variables provided in the schemes below are defined in accordance with the description of compounds of Formula (I) unless otherwise specified. Where a variable has been further defined in any one scheme below, said variable should assume the same values in subsequent schemes unless yet further defined. The definitions of compounds in the schemes below are not intended to narrow the scope of compounds described by Formula (I). Moreover, the schemes provided herein may be modified in a manner apparent to one skilled in the art to describe additional processes for making compounds of the present invention.

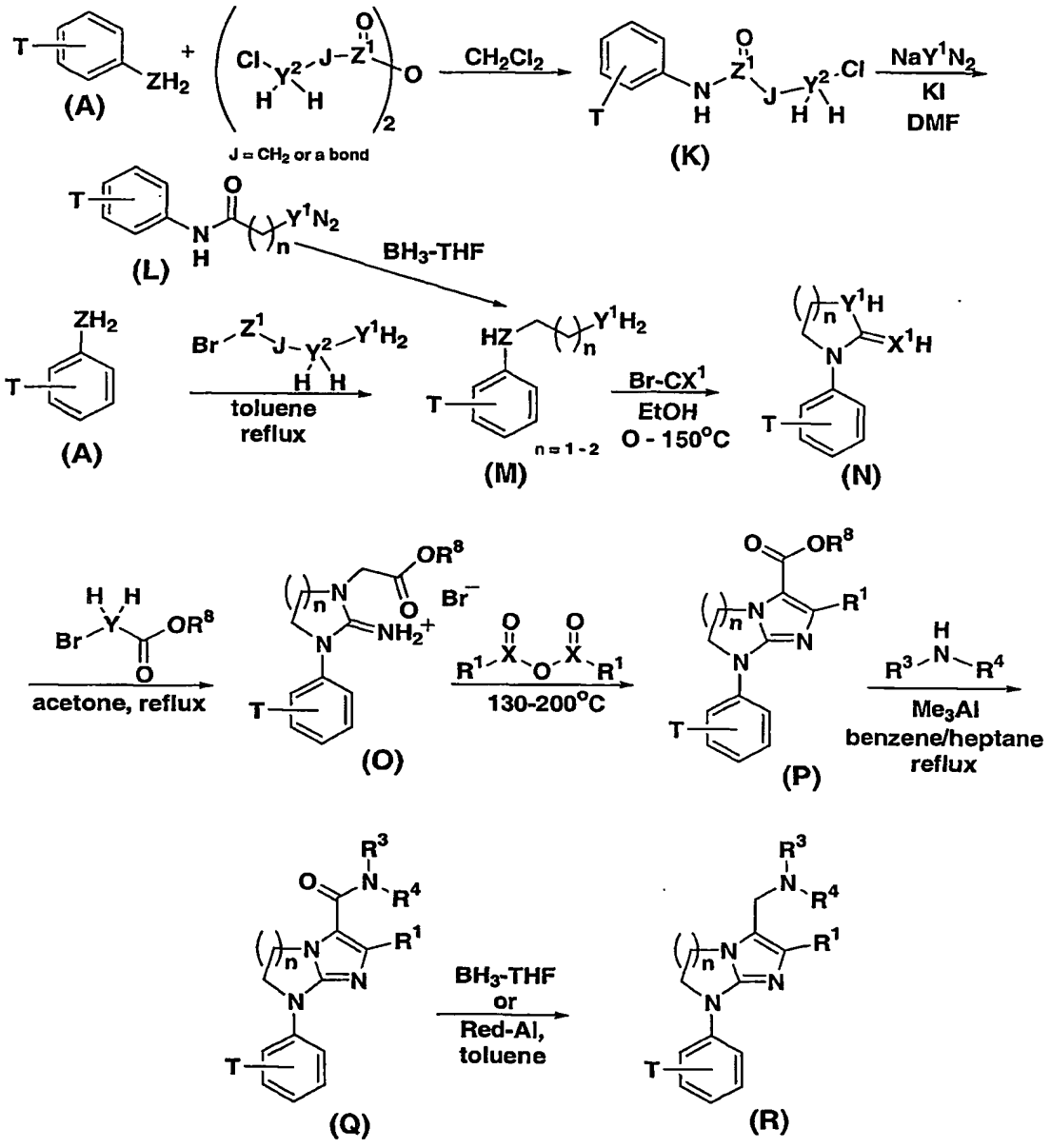
Scheme 1


(A)
(A) = V-NH2, including 2- and 3-pyridyl
T = substitutions of V
Z = N
KF, 140-180°C
LG = F, Cl
K-L=M-Q is E1-E3
Y2 and Z1 = C
Y1 = N
(B)
H2, Pd-C or Na2S2O4
(C)
Br-CX1
EtOH
O - 150°C
X1 = N
(D)
acetone, reflux
R8 = C1-C6 alkyl
(E)
130-200°C
X = C
(F)
Me3Al
benzene/heptane
reflux
(G)
BH3-THF or Red-Al, toluene
(H)

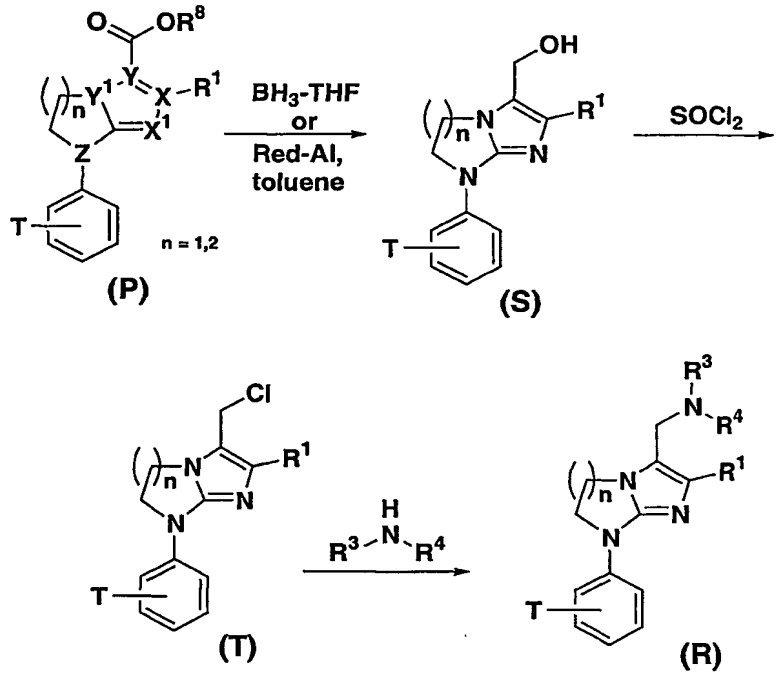
Scheme 2


R8O
O
R1
X
Y
Y1
Y2
K=L
M
X1
Z1
Q
Z
T
(F)
K-L=M-Q
is E1-E3
BH3-THF
or
Red-Al,
toluene
OH
R1
N
K=L
M
Q
T
(I)
SOCl2
Cl
(J)
H
N
R3
R4
R3
N
R4
(H)

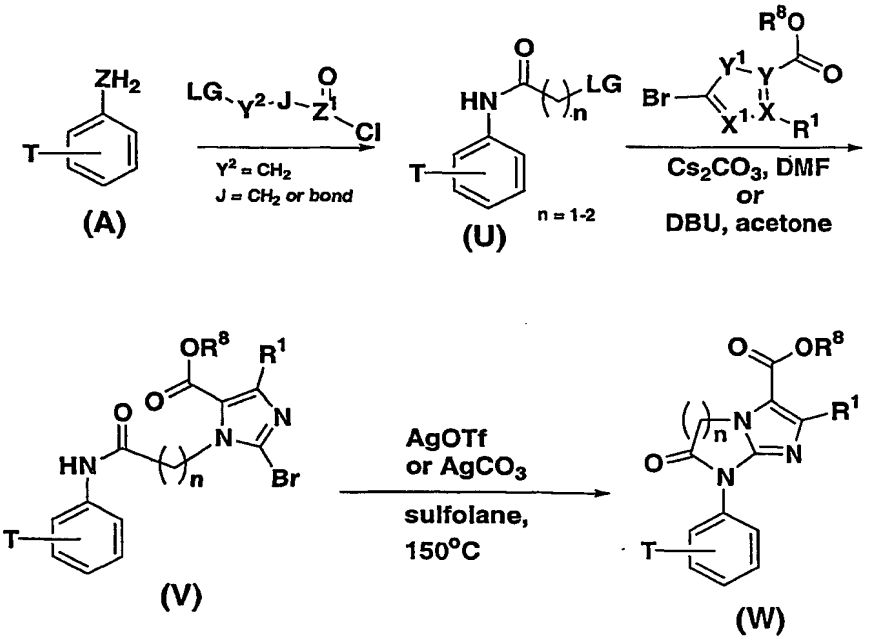
Scheme 3


(A)
J = CH2 or a bond
CH2Cl2
(K)
NaY1N2
KI
DMF
(L)
BH3-THF
toluene
reflux
(M)
n = 1 - 2
Br-CX1
EtOH
0 - 150°C
(N)
acetone, reflux
(O)
130-200°C
(P)
Me3Al
benzene/heptane
reflux
(Q)
BH3-THF
or
Red-Al,
toluene
(R)

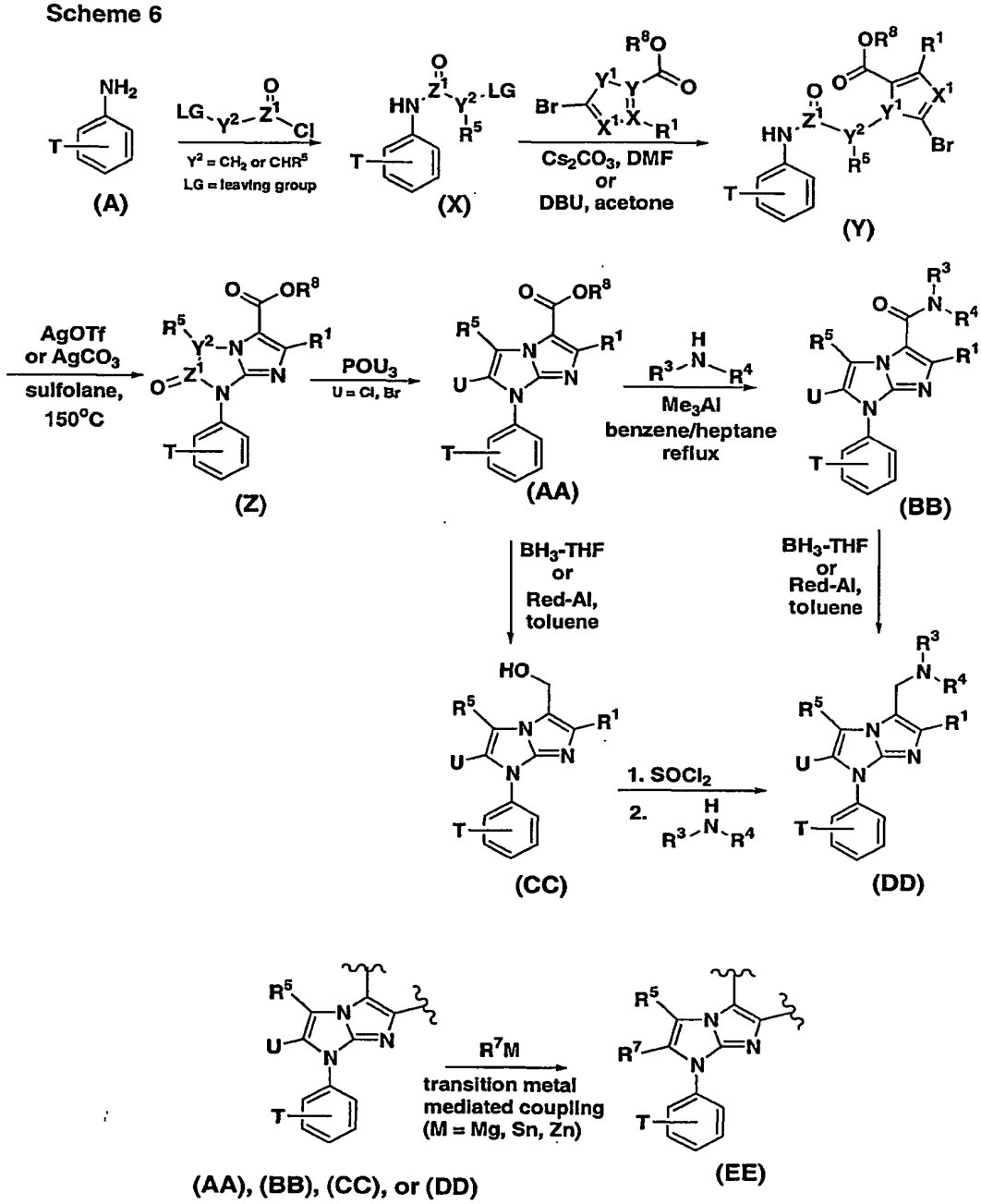
Scheme 4



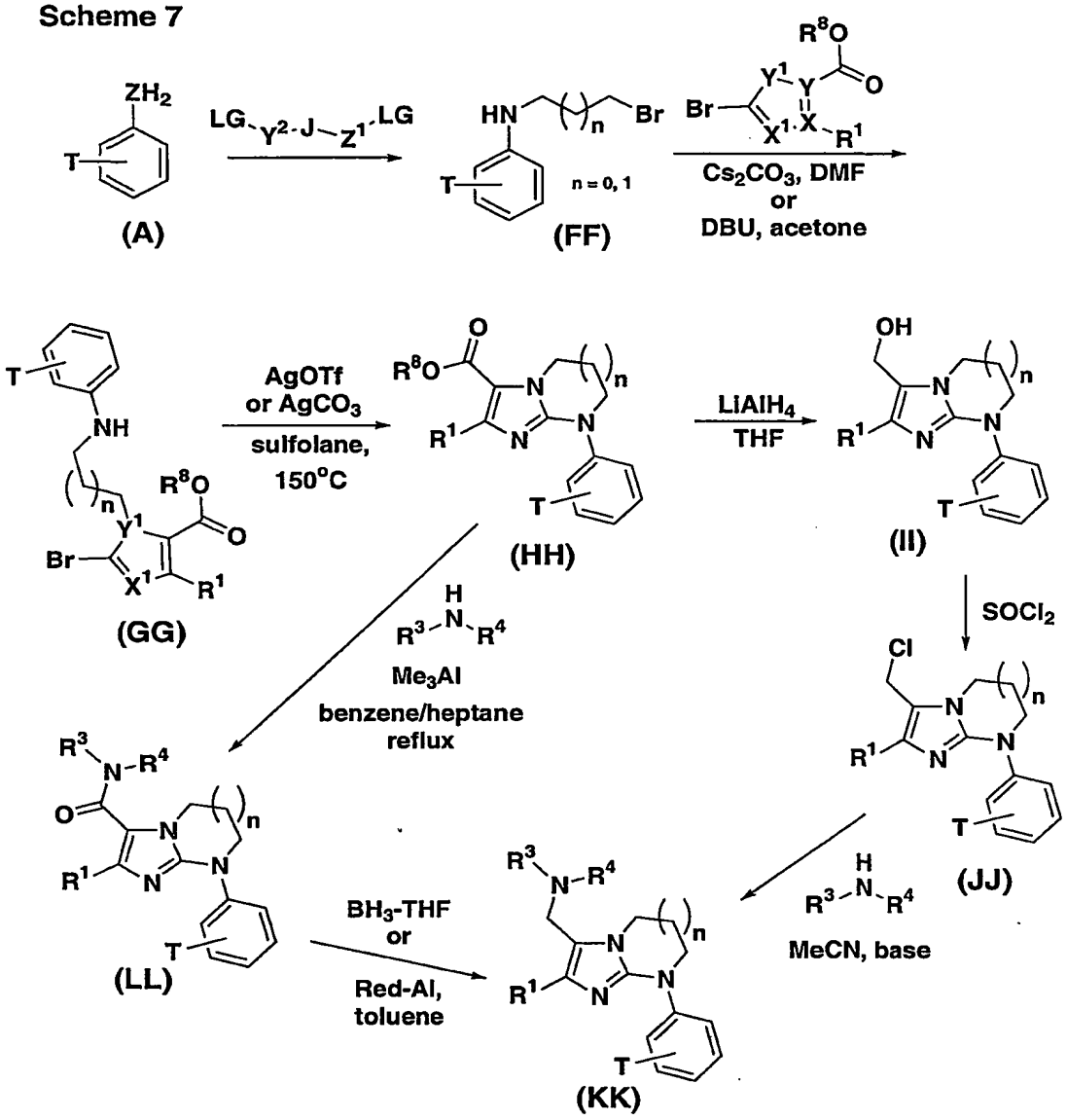
Scheme 5



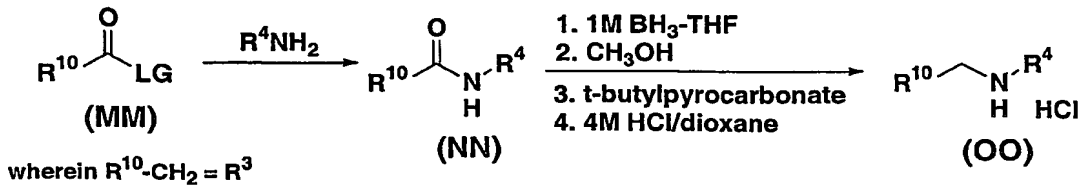
Scheme 6


(A)
LG-Y2-Z1(=O)-Cl
Y2 = CH2 or CHR5
LG = leaving group
(X)
Cs2CO3, DMF
or
DBU, acetone
(Y)
AgOTf
or AgCO3
sulfolane,
150°C
(Z)
POU3
U = Cl, Br
(AA)
Me3Al
benzene/heptane
reflux
(BB)
BH3-THF
or
Red-Al,
toluene
BH3-THF
or
Red-Al,
toluene
(CC)
1. SOCl2
2.
(DD)
R7M
transition metal
mediated coupling
(M = Mg, Sn, Zn)
(AA), (BB), (CC), or (DD)
(EE)

Scheme 7



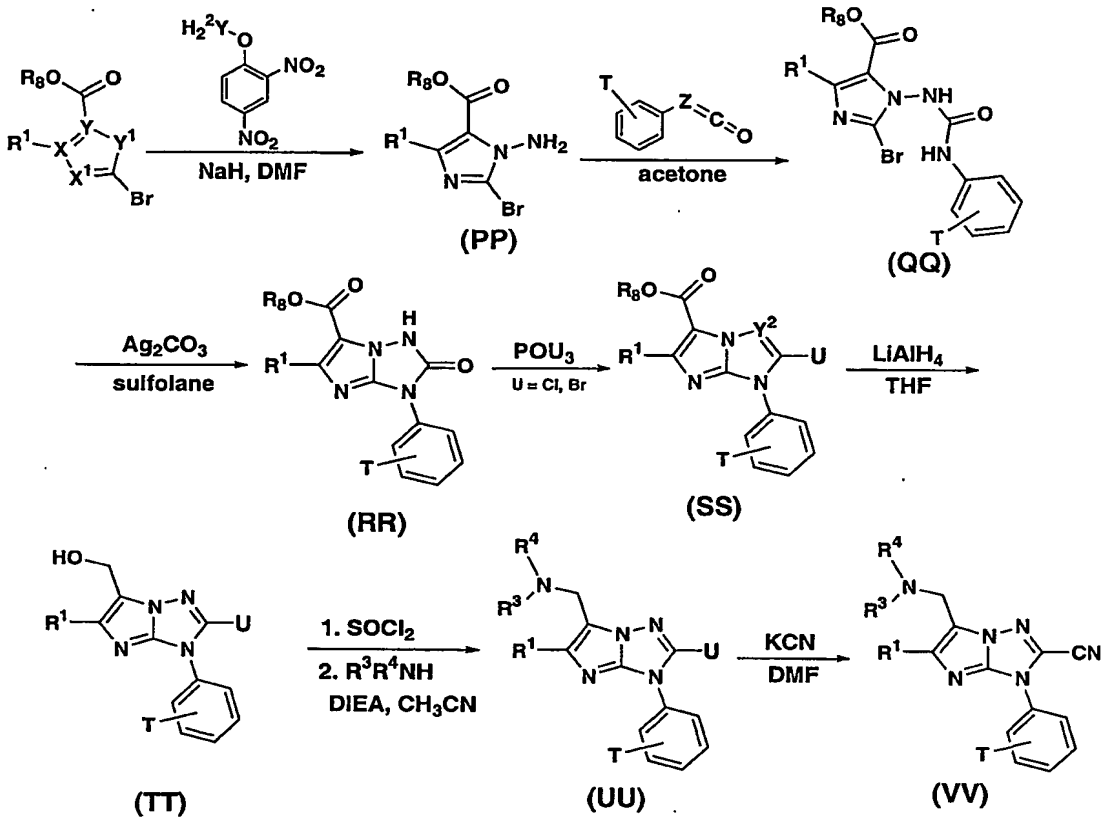
Scheme 8



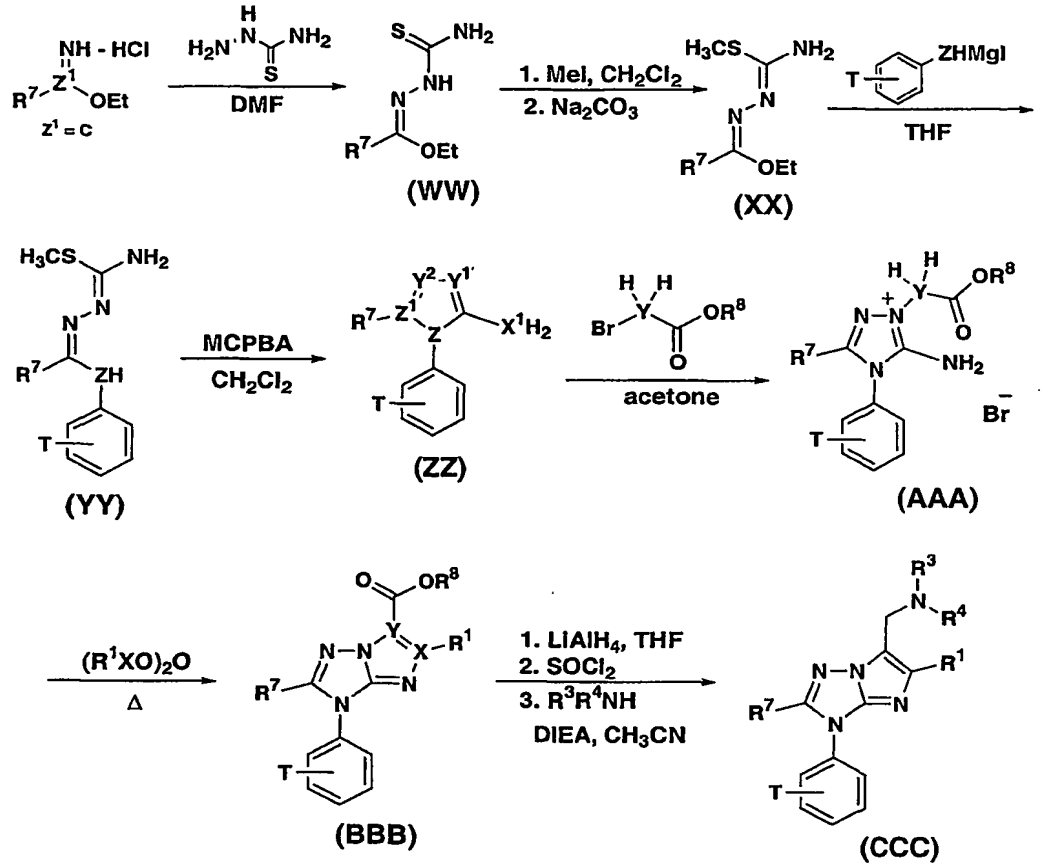
wherein R^{10}-CH_2 = R^3

LG = leaving group

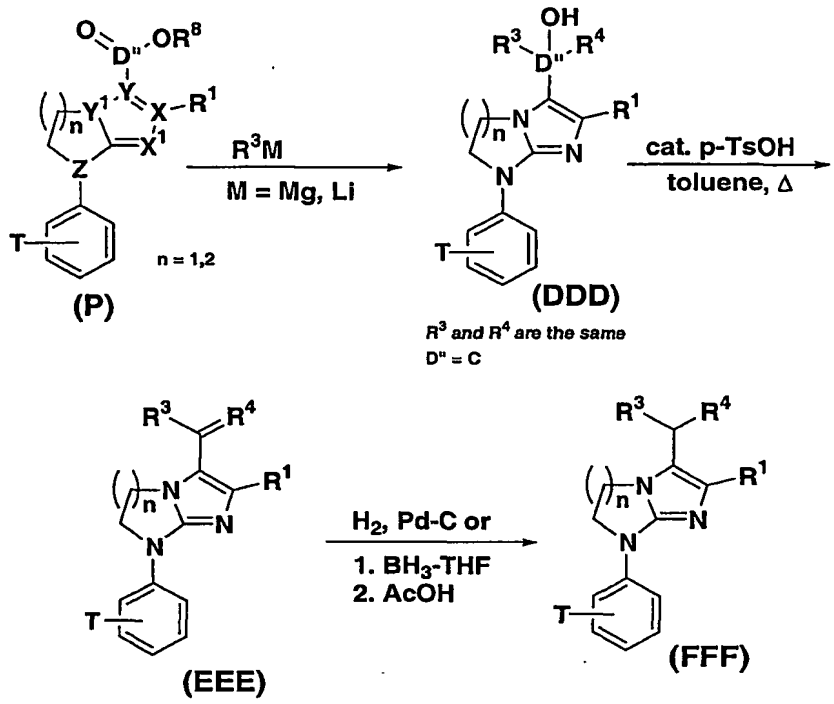
Scheme 9


NaH, DMF
acetone
(PP)
(QQ)
Ag_2CO_3
sulfolane
POU_3
U = Cl, Br
$LiAlH_4$
THF
(RR)
(SS)
1. $SOCl_2$
2. R^3R^4NH
DIEA, CH_3CN
KCN
DMF
(TT)
(UU)
(VV)

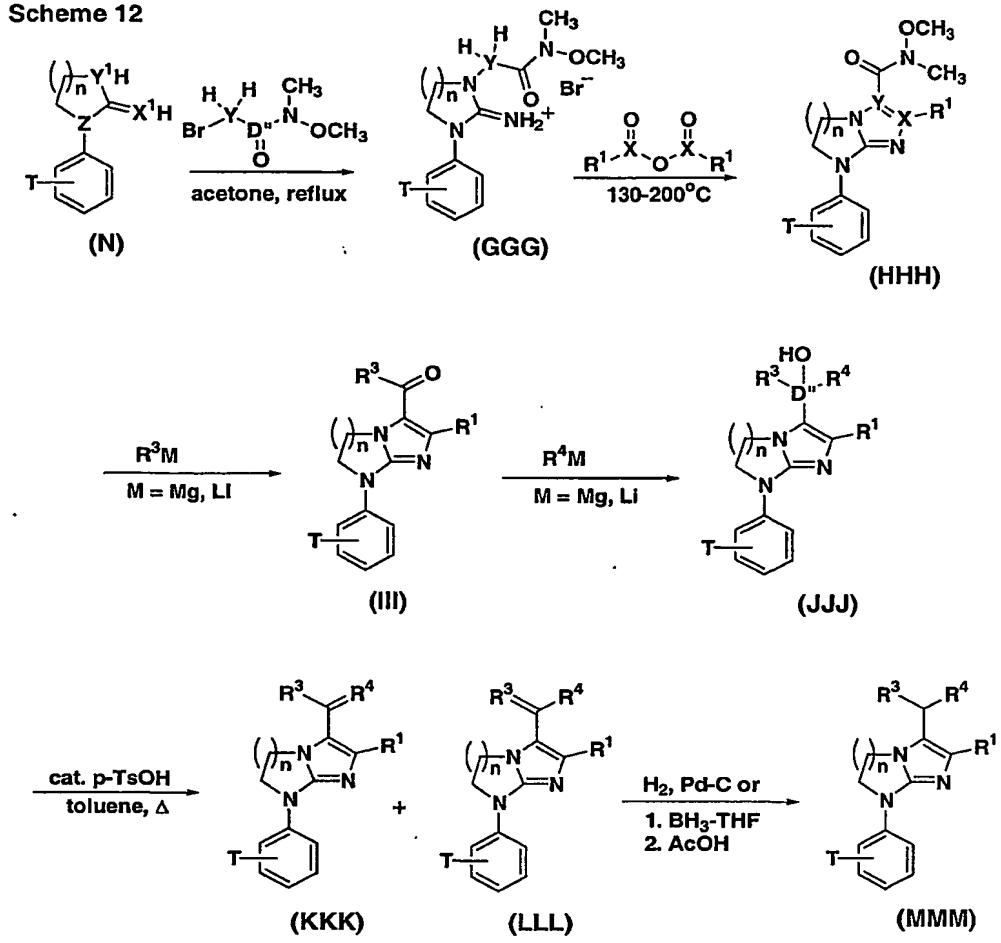
Scheme 10


NH - HCl
R7
Z1
OEt
Z1 = C
DMF
(WW)
1. MeI, CH2Cl2
2. Na2CO3
(XX)
ZHMgI
THF
(YY)
MCPBA
CH2Cl2
(ZZ)
acetone
Br
(AAA)
(R1XO)2O
Δ
(BBB)
1. LiAlH4, THF
2. SOCl2
3. R3R4NH
DIEA, CH3CN
(CCC)

Scheme 11

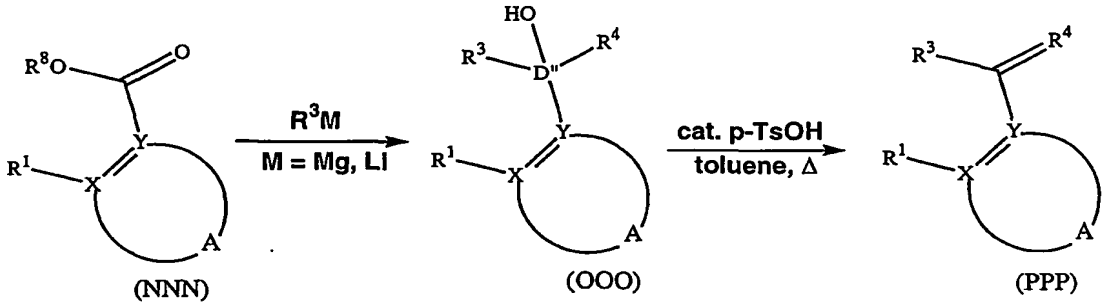

R3M
M = Mg, Li
cat. p-TsOH
toluene, Δ
n = 1,2
(P)
(DDD)
R3 and R4 are the same
D" = C
H2, Pd-C or
1. BH3-THF
2. AcOH
(EEE)
(FFF)

Scheme 12

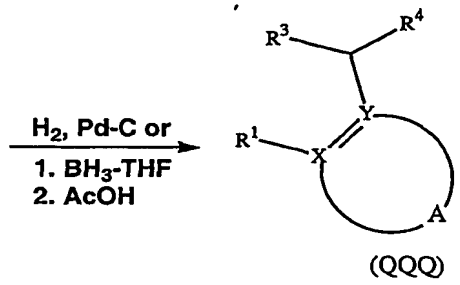


(N) (GGG) (HHH) (III) (JJJ) (KKK) (LLL) (MMM)

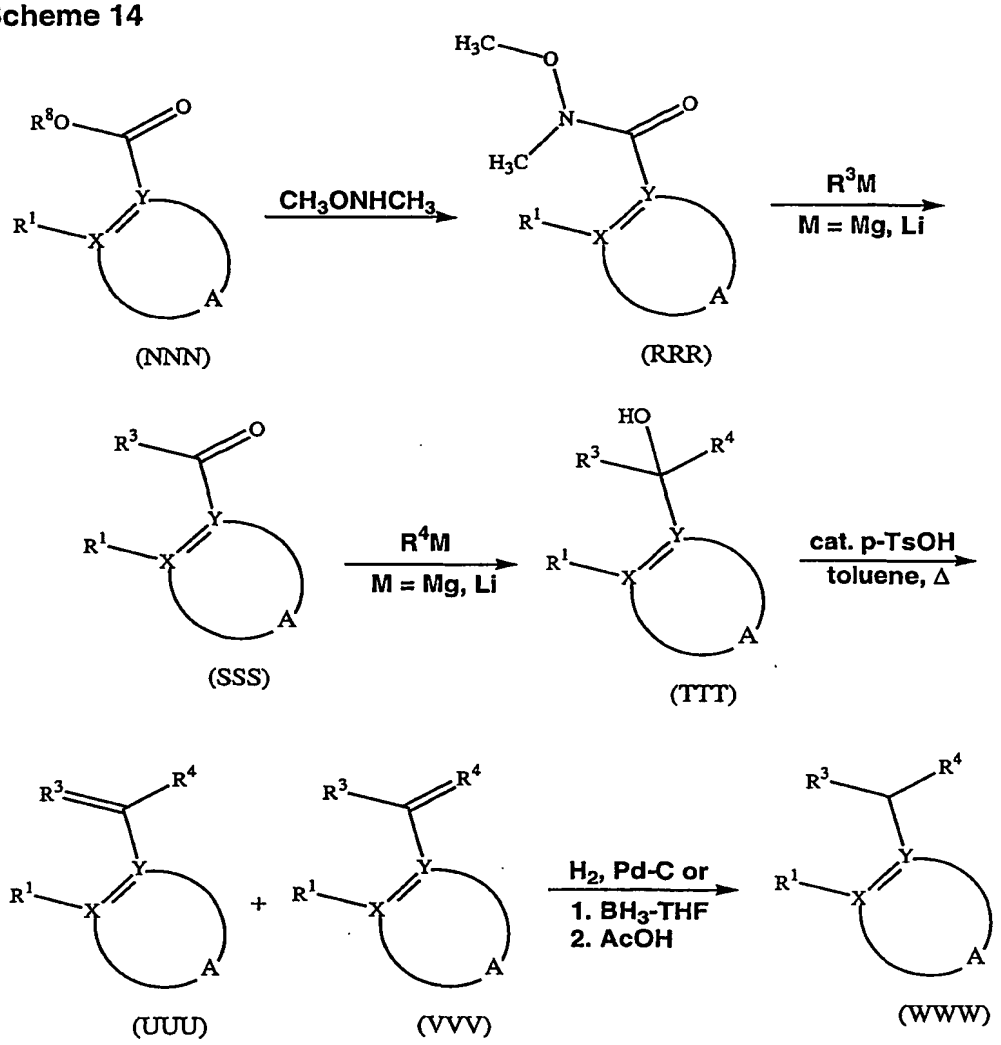
Scheme 13



R^3 and R^4 are the same



Scheme 14

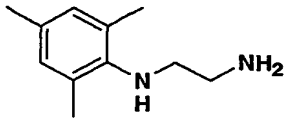

R^8O
O
Y
R^1
X
A
(NNN)
CH_3ONHCH_3
H_3C
O
N
H_3C
O
Y
R^1
X
A
(RRR)
R^3M
M = Mg, Li
R^3
O
Y
R^1
X
A
(SSS)
R^4M
M = Mg, Li
HO
R^3
R^4
Y
R^1
X
A
(TTT)
cat. p-TsOH
toluene, Δ
R^3
R^4
Y
R^1
X
A
(UUU)
+
R^3
R^4
Y
R^1
X
A
(VVV)
H_2, Pd-C or
1. BH_3-THF
2. AcOH
R^3
R^4
Y
R^1
X
A
(WWW)

Other suitable means of synthesizing said compounds may also be available. More detailed descriptions of synthesizing compounds of the present invention are also provided as follows:

General. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were run on a Bruker 500 or 300 MHz instrument and chemical shifts were reported in ppm (δ) with reference to $(CH_3)_4Si$. All evaporations were carried out under reduced pressure. Unless otherwise stated, LC/MS analyses were carried out on a Shimadzu instrument using a YMC C18 column (3 x 50 mm) employing a 2 min linear gradient of 0% to100% solvent B in A in a 3 min run. For LC/MS and for Shimadzu Preparative HPLC system, Solvent A-was:10% methanol/90% water/0.1% trifluoroacetic acid, and solvent B was 90% methanol/10% water/0.1% trifluoroacetic acid with a UV detector set at 220 nm.

The following **Intermediates 1-5** may be used to synthesize **Examples 1-26.**

Intermediate 1

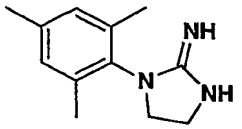


N^1-(2,4,6-Trimethyl-phenyl)-ethane-1,2-diamine, scheme 3: (M)

To a solution of 2,4,6-trimethylaniline (100. g, 0.740 mol) in anhydrous toluene (600 mL) was added 2-bromoethylamine hydrobromide (75.8 g, 0.370 mol). The flask containing the reaction mixture was fitted with a Dean-Stark trap/reflux condenser assembly. The reaction mixture was heated at reflux temperature for 5 h, during which time the mixture solidified. Upon cooling to room temperature, the solidified mass was treated with water (240 mL), toluene (160 mL), and 50% aqueous KOH (80 mL). The phases were separated, and the aqueous portion was saturated with NaCl and extracted with toluene

(2 X 200 mL). The combined organic portions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to remove the solvent. Vacuum distillation (2 mm Hg) afforded 42.4 g of a light yellow liquid, which was 92% pure based on ^1H NMR. Eight per cent of the material was unreacted 2,4,6-trimethylaniline. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 2H), 3.00 – 2.96 (m, 2H), 2.92 – 2.88 (m, 2H), 2.28 (s, 6H), 2.23 (s, 3H), 2.21 (s, 1H), 2.16 (s, 2H). LC/MS: t_R = 0.87 min., (MH^+) = 179.19.

Intermediate 2

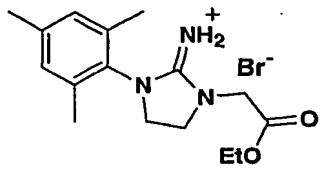


1-(2,4,6-Trimethyl-phenyl)-4,5-dihydro-1*H*-imidazol-2-ylamine, scheme 3: (N)[1]

A solution of cyanogen bromide (1.8 g, 18.5 mmol) in anhydrous ethanol (3 mL) was added at 0°C to a solution of N^1-(2,4,6-trimethyl-phenyl)-ethane-1,2-diamine (3.0 g, 16.9 mmol) in anhydrous ethanol (9 mL) under nitrogen. The reaction mixture was warmed up to room temperature for 10 min, then was heated at 155 °C for 40 min with a flow of nitrogen to remove ethanol. Upon cooling to r.t., the resulting solids were transferred to a separatory funnel via dichloromethane (70 mL), and washed sequentially with 1 N sodium hydroxide (2 × 35 mL), water and brine. The organic layer was dried over anhydrous sodium sulfate and solvents were removed in vacuo to afford the title compound as a pale white solid (3.08 g, 90% yield). The solids were used for the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.70 (s, 2H), 3.46 (s, 4H), 2.06 (s, 3H), 1.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

160.1, 138.2, 137.8, 132.2, 129.5, 48.8, 43.5, 20.8, 17.5. LC/MS: t_R = 0.99 min., (MH^+) = 204.12.

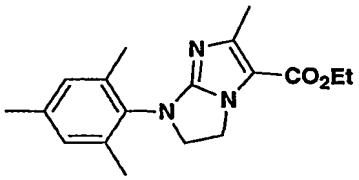
Intermediate 3



3-Ethoxycarbonylmethyl-1-(2,4,6-trimethyl-phenyl)-2-aminoimidazolium bromide, scheme 3: (O)

To a mixture of 1-(2,4,6-trimethyl-phenyl)-imidazolidin-2-ylideneamine (3.00 g, 0.0148 mol) and aluminum tri-*tert*-butoxide (1.0 g, 0.0041 mol) in dimethylformamide (15 mL) was added ethyl bromoacetate (1.65 mL, 2.48 g, 0.00148 mol). The reaction mixture was allowed to stir at room temperature for 1 h, after which LC-MS indicated a 4:1 ratio of desired product to starting material. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a pale orange-yellow solid, which was then treated twice with toluene to azeotropically remove any water. The solid was triturated with toluene, collected by filtration, and placed under high vacuum for 6 h. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (s, 2H), 4,87 (s, 2H), 4.29 (q, J = 7 Hz, 2H), 3.96 – 3.89 (m, 4H), 2.32 (s, 3H), 2.25 (s, 6H), 1.34 (t, J = 7 Hz, 3H). LC/MS: t_R = 0.92 min., (MH^+) = 290.43.

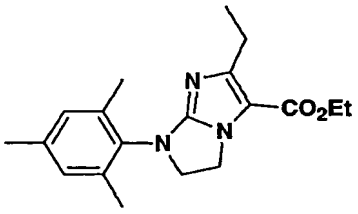
Intermediate 4



2-Methyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazole-3-carboxylic acid ethyl ester, (scheme 3: (P)^2

A mixture of 3-ethoxycarbonylmethyl-1-(2,4,6-trimethyl-phenyl)-2-aminoimidazolium bromide (1.0 g, 2.7 mmol), sodium acetate (0.55 g, 6.75 mmol) and acetic anhydride (5.0 mL) was heated at 160 °C for 12 hr. Upon cooling, the mixture was poured into a flask containing ice. While stirring, excess sodium bicarbonate was added to the above mixture in small portions, and the resulting mixture was stirred at room temperature for 6 hr. Then, the mixture was extracted with dichloromethane (2 × 40 mL). The organic extracts were washed with water and dried over anhydrous sodium sulfate. Solvents were removed in vacuo and the residue was subjected to chromatography using ethyl acetate/hexanes (1:4) as eluent to afford the title compound as a light yellow oil which solidified upon cooling (0.344 g, 41% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.36 – 4.26 (m, 2H), 4.15 – 4.08 (m, 2H), 2.39 (s, 3H), 2.26 (s, 3H), 2.20 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). Mass spec.: 314.15 (MH^+).

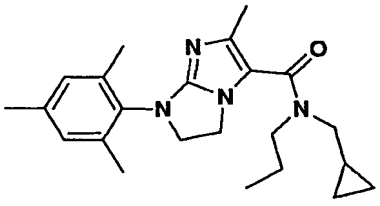
Intermediate 5



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-3-carboxylic acid ethyl ester, scheme 3: (P)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (s, 2H), 4.36 (t, J = 8.4 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.14 (t, J = 8.4 Hz, 2H), 2.81 (q, J = 7.4 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.5 Hz, 3H). LC/MS: t_R = 1.35 min., (MH^+) = 328.19.

Example 1

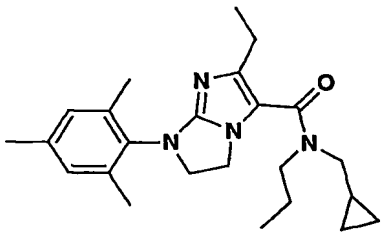


2-Methyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

A solution of trimethyl aluminum (2.0 M in heptane, 2.2 mL, 4.4 mmol) was added to a solution of N-cyclopropylmethyl-N-propylamine (0.63 mL, 4.4 mmol) in benzene (3 mL) at 0°C. The mixture was warmed up to room temperature and stirred at this temperature for 1.5 h, and then added to a stirred solution of 2-methyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-3-carboxylic acid ethyl ester (0.172 g, 0.55 mmol) in benzene (8.0 mL). The mixture was refluxed for

12 h. Upon cooling at 0°C, 1 N sodium hydroxide (25 mL) was added dropwise to the above mixture. The mixture was extracted with dicholoromethane (40 mL), and the organic layer was dried over anhydrous sodium sulfate. Solvents were removed in vacuo and the residue was subjected to chromatography using ethyl acetate/hexanes (1:1) as eluent to afford the title compound as a light yellow oil which solidified upon cooling (0.209 g, 100% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 156.0, 141.0, 136.5, 136.1, 132.7, 128.7, 115.8, 52.6, 50.3, 47.1, 42.1, 20.1, 19.9, 17.3, 14.6, 10.3, 9.2, 2.8. Mass spec.: 381.26 (MH^+).

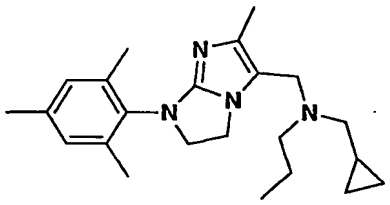
Example 2



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 2H), 4.12 – 4.01 (m, 4H), 3.56 (t, J = 7.1 Hz, 2H), 3.35 (d, J = 6.8 Hz, 2H), 2.42 (q, J = 7.5 Hz, 2H), 2.21 (s, 3H), 2.17 (s, 6H), 1.59 (quintet, J = 7.2 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H), 0.99 – 0.95 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H), 0.51 – 0.48 (m, 2H), 0.17 – 0.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1, 156.9, 147.6, 137.3, 136.9, 133.9, 129.6, 115.6, 53.6, 51.2, 48.1, 42.9, 22.6, 21.0, 20.9, 18.2, 13.7, 11.3, 10.0, 3.75. LC/MS: t_R = 1.36 min., (MH^+) = 395.27.

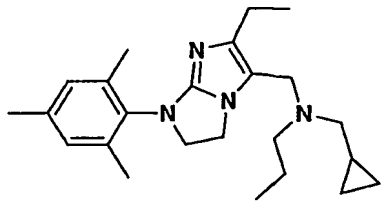
Example 3



Cyclopropylmethyl-[2-methyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazol-3-ylmethyl]-propyl-amine, scheme 3: (R)

A solution of Red-Al (3.3 M in toluene, 0.70 mL, 2.33 mmol) was added dropwise to a solution of 2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide (0.177 g, 0.46 mmol) in toluene (3 mL) at 0°C. After stirring at room temperature for 24 h, the reaction mixture was cooled to 0°C and I N sodium hydroxide (10 mL) was added dropwise. The above mixture was extracted with dichloromethane (40 mL), and the organic extracts were washed with water and dried over anhydrous sodium sulfate. Solvents were removed in vacuo to afford the title compound as a light yellow oil which solidified upon cooling (109 mg, 65% yield). The purity of the product was determined to be 91% by LC/MS. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (s, 2H), 4.09 – 3.96 (m, 4H), 3.45 (s, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.29 (d, J = 6.5 Hz, 2H), 2.23 (s, 3H), 2.19 (s, 6H), 2.04 (s, 3H), 1.46 (quintet, J = 7.3 Hz, 2H), 1.28 – 1.25 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H), 0.49 – 0.46 (m, 2H), 0.09 – 0.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 137.1, 136.9, 136.0, 135.0, 129.7, 117.7, 58.5, 55.5, 53.8, 48.0, 42.4, 20.9, 20.3, 18.2, 13.3, 12.0, 8.9, 4.0. Mass spec.: 367.24 (MH^+).

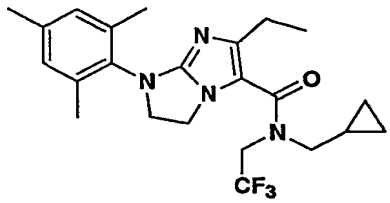
Example 4



Cyclopropylmethyl-[2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]imidazol-3-ylmethyl]-propyl-amine, scheme 3: (R)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 2H), 4.13 – 3.97 (m, 4H), 3.47 (s, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.39 (q, J = 7.6 Hz, 2H), 2.31 (d, J = 6.5 Hz, 2H), 2.24 (s, 3H), 2.19 (s, 6H), 1.48 – 1.42 (m, 2H), 1.32 – 1.26 (m, 1H), 1.06 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.50 – 0.46 (m, 2H), 0.09 – 0.07 (m, 2H). Mass spec.: 381.28 (MH^+).

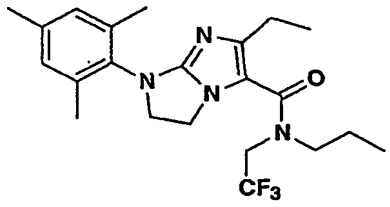
Example 5



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.51 min., (MH^+) = 435.36.

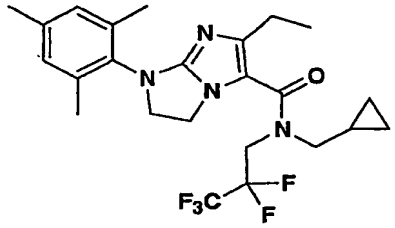
Example 6



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid propyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.25 min., (MH^+) = 423.37.

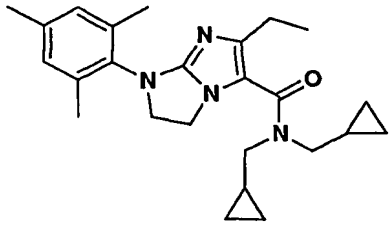
Example 7



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(3,3,3,2,2-pentafluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.43 min., (MH^+) = 485.35.

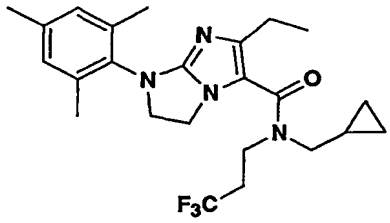
Example 8



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(cyclopropylmethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.28 min., (MH^+) = 407.42.

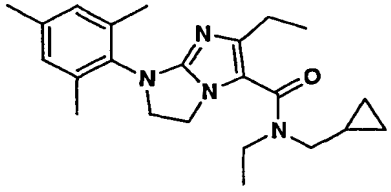
Example 9



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.28 min., (MH^+) = 449.37.

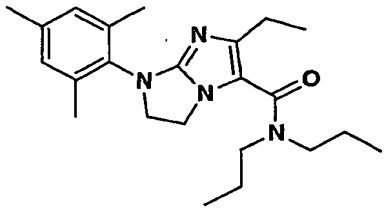
Example 10



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.41 min., (MH^+) = 381.36.

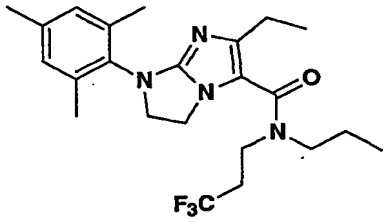
Example 11



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid dipropyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.26 min., (MH^+) = 383.41.

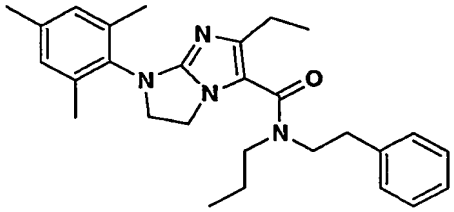
Example 12



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid propyl-(3,3,3-trifluoropropyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.28 min., (MH^+) = 437.33.

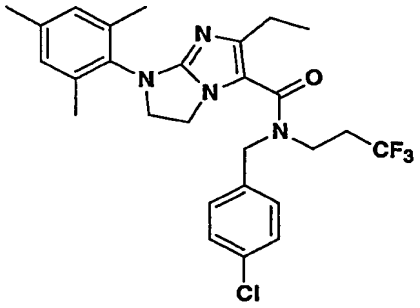
Example 13



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid phenethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.45 min., (MH^+) = 445.37.

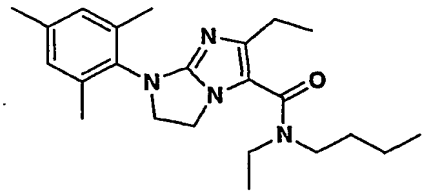
Example 14



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (4-chloro-benzyl)-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.48 min., (MH^+) = 519.35.

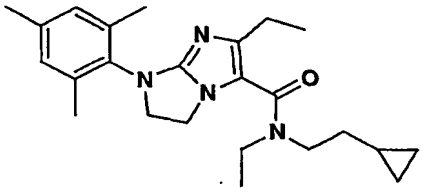
Example 15



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid butyl-ethyl-amide, scheme 3: (Q)

Prepared as described for the example above, except that N-ethylbutylamine was used rather than its HCl salt. LC/MS: t_R = 1.41 min., (MH^+) = 383.37.

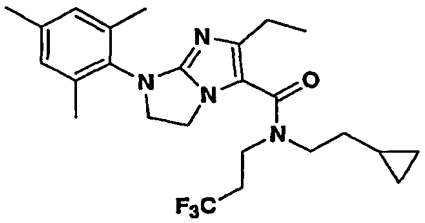
Example 16



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (2-cyclopropyl-ethyl)-ethyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.38 min., (MH^+) = 395.45.

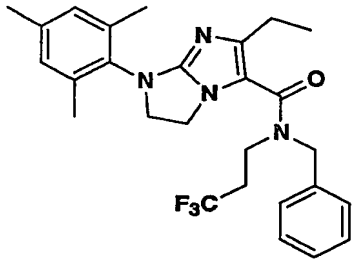
Example 17



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (2-cyclopropyl-ethyl)-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.33 min., (MH^+) = 395.45.

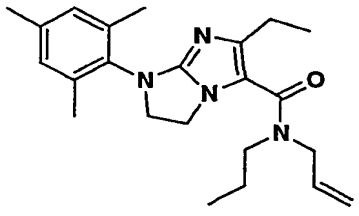
Example 18



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid benzyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.51 min., (MH^+) = 485.39.

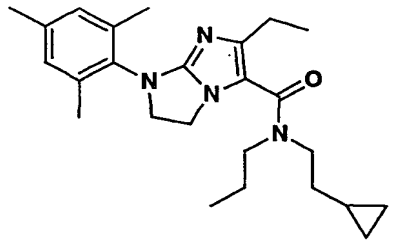
Example 19



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid allyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.31 min., (MH^+) = 381.36.

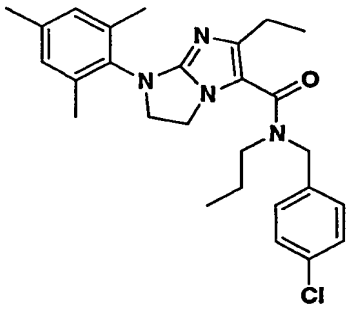
Example 20



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (2-cyclopropyl-ethyl)-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.33 min., (MH^+) = 409.43.

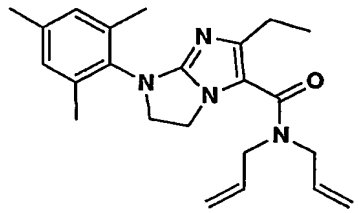
Example 21



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (4-chloro-benzyl)-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.40 min., (MH^+) = 465.35.

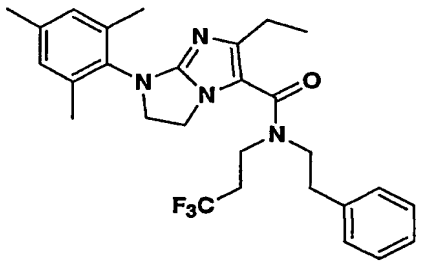
Example 22



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid diallylamide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.39 min., (MH^+) = 379.40.

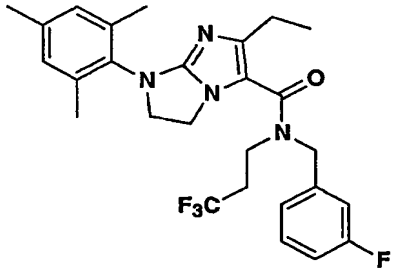
Example 23



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid phenethyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.39 min., (MH^+) = 499.38.

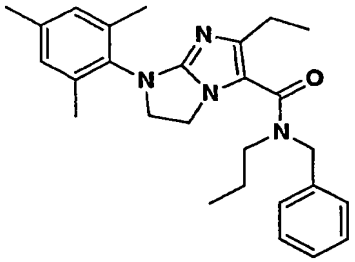
Example 24



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (3-fluoro-benzyl)-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.50 min., (MH^+) = 503.17.

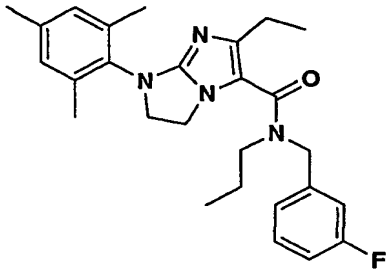
Example 25



2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid benzyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.41 min., (MH^+) = 431.34.

Example 26

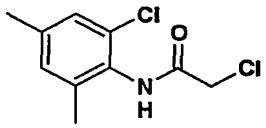


2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid (3-fluoro-benzyl)-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.38 min., (MH^+) = 449.35.

The following **Intermediates 6-10** may be used to synthesize **Examples 27-29.**

Intermediate 6

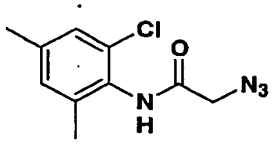


2-Chloro-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide, scheme 3: (K)

To a solution of 2-chloro-4,6-dimethylaniline (0.300 g, 0.00193 mol) in dichloroethane (6 mL) was added chloroacetic anhydride (0.460 g, 0.0027 mol). The reaction was allowed to stir at room temperature for 1 h and was then quenched with saturated aqueous $NaHCO_3$ and allowed to stir for another 15 min. The reaction mixture was extracted with ethyl acetate (2 X 15 mL), and the combined organic portions were washed sequentially with saturated aqueous $NaHCO_3$ and brine. After drying over anhydrous Na_2SO_4, the organic portion was concentrated under reduced pressure to give 0.40 g (0.0017 mol, 90%) of white solid. ^1H NMR ($CDCl_3$, 300

MHz) δ 7.94 (br s, 1H), 7.12 (s, 1H), 6.98 (s, 1H), 4.25 (s, 2H), 2.3 (s, 3H), 2.24 (s, 3H). LC/MS: t_R = 1.22 min., (MH^+) = 232.02.

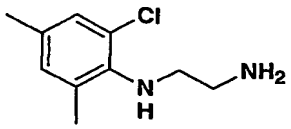
Intermediate 7



2-Azido-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide, scheme 3: (L)

A mixture of 2-Chloro-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide (0.100 g, 0.00043 mol), potassium iodide (0.0072 g, 0.00043 mol), sodium azide (0.056 g, 0.00086 mol), and anhydrous dimethylformamide (7 mL) was heated in a 50°C oil bath for 4 h. Upon cooling to room temperature, the reaction mixture was cooled to 0°C, water (10 mL) was added, and the solid product was collected by suction filtration, washed several times with water, and placed in a vacuum oven set at low heat for 4 h. The dried product amounted to 0.0934 g (0.391 mmol, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (br s 1H), 7.12 (s, 1H), 6.98 (s, 1H), 4.2 (s, 2H), 2.3 (s, 3H), 2.23 (s, 3H). LC/MS: t_R = 1.23 min., (MH^+) = 239.06.

Intermediate 8

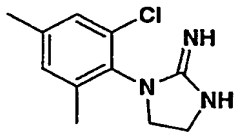


N^1-(2-Chloro-4,6-dimethyl-phenyl)-ethane-1,2-diamine, scheme 3: (M)

2-Azido-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide (0.210 g, 0.00126 mol) was dissolved in cold 1.0 M BH_3- tetrahydrofuran (7.6 mL), and the reaction mixture was allowed to stand for approximately 15 min. and was then heated at reflux temperature

for 14 h. Upon cooling to room temperature, the reaction was quenched with excess methanol, and the solvents were removed *in vacuo*. The residue was dissolved in 10 mL 1:1 methanol:10% aqueous HCl and heated at reflux temperature for 3 h. Upon cooling to room temperature, the reaction solution was basified with 2 N aqueous NaOH and extracted with ethyl acetate (3 X 20 mL). The combined organic portions were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 0.220 g (0.00111 mol, 88%) of pale yellow liquid. ^{1}H-NMR δ ($CDCl_3$, 300 MHz) 2.22 (s, 3H), 2.29 (s, 3H), 2.86 (t, 2H), 3.06 (t, 2H), 6.84 (d, 1H), 6.99 (d, 1H). LC/MS: t_R = 1.90 min., (MH^+) = 199.08.

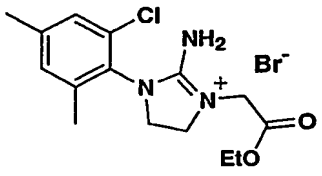
Intermediate 9



1-(2-Chloro-4,6-dimethyl-phenyl)-imidazolidin-2-ylideneamine, scheme 3: (N)

Prepared as described for 1-(2,4,6-trimethyl-phenyl)-imidazolidin-2-ylideneamine. ^{1}H-NMR δ ($CDCl_3$, 300 MHz) 2.22 (s, 3H), 2.26 (s, 3H), 3.63 (m, 1H), 3.73 (m, 2H), 3.86 (m, 1H), 6.07 (br, 2H), 6.96 (s, 1H), 7.08 (s, 1H). LC/MS: t_R = 0.87 min., (MH^+) = 224.15.

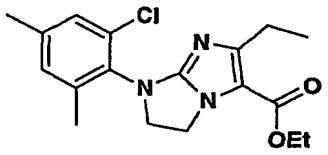
Intermediate 10



3-Ethoxycarbonylmethyl-1-(2-chloro-4,6-dimethyl-phenyl)-2-aminoimidazolium bromide, scheme 3: (O)

Prepared as described for 3-ethoxycarbonylmethyl-1-(2,4,6-trimethyl-phenyl)-2-aminoimidazolium bromide. LC/MS: t_R = 0.98 min., (MH^+) = 310.17.

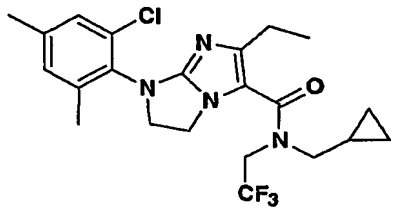
Intermediate 11



7-(2-Chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester, scheme 3: (P)

Prepared as described for 2-ethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester. LC/MS: t_R = 1.33 min., (MH^+) = 348.17.

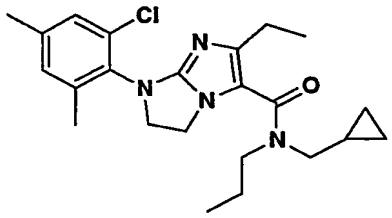
Example 27



7-(2-Chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for 2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide. LC/MS: t_R = 1.36 min., (MH^+) = 455.19.

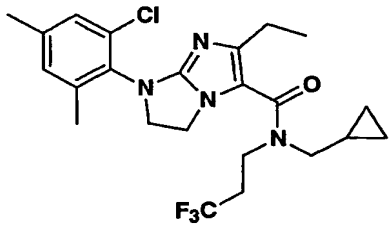
Example 28



7-(2-Chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.41 min., (MH^+) = 415.24.

Example 29



7-(2-Chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.38 min., (MH^+) = 469.20.

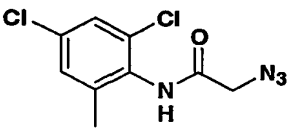
The following **Intermediates 12-17** may be used to synthesize **Examples 30-33.**

Intermediate 12

2-Chloro-N-(2,4-dichloro-6-methyl-phenyl)-acetamide, scheme 3: (K)

Prepared as described for 2-chloro-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide. Mass spec.: 253.94 (MH^+).

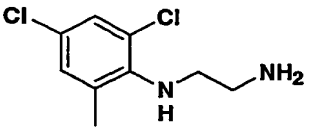
Intermediate 13



2-Azido-N-(2,4-dichloro-6-methyl-phenyl)-acetamide, scheme 3: (L)

Prepared as described for 2-azido-N-(2-chloro-4,6-dimethyl-phenyl)-acetamide.

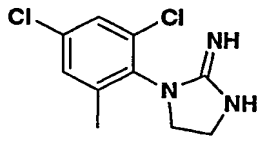
Intermediate 14



N^1-(2,4-Dichloro-6-methyl-phenyl)-ethane-1,2-diamine, scheme 3: (M)

Prepared as described for N^1-(2-chloro-4,6-dimethyl-phenyl)-ethane-1,2-diamine. ^{1}H-NMR δ ($CDCl_3$, 300 MHz) 2.28 (s, 3H), 2.84 (t, 2H), 3.07 (t, 2H), 6.98 (d, 1H), 7.15 (d, 1H); Mass spec.: 219.04 (MH^+).

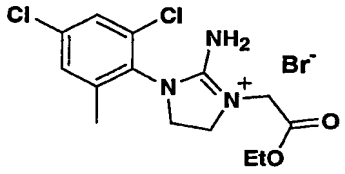
Intermediate 15



1-(2,4-Dichloro-6-methyl-phenyl)-imidazolidin-2-ylideneamine, scheme 3: (N)

Prepared as described for 1-(2-chloro-4,6-dimethyl-phenyl)-imidazolidin-2-ylideneamine. Mass spec.: 244.03 (MH^+).

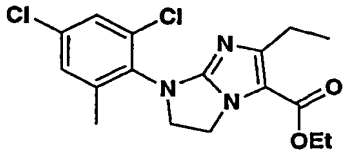
Intermediate 16



3-Ethoxycarbonylmethyl-1-(2,4-chloro-6-methyl-phenyl)-2-aminoimidazolium bromide, scheme 3: (O)

Prepared as described for 3-ethoxycarbonylmethyl-1-(2-chloro-4,6-dimethyl-phenyl)-2-aminoimidazolium bromide. LC/MS: t_R = 1.12 min., (MH^+) = 410.05.

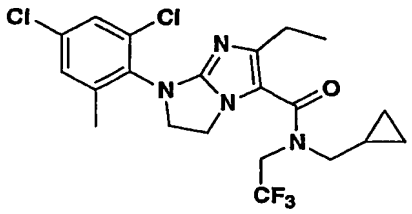
Intermediate 17



7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester, scheme 3: (P)

Prepared as described for 7-(2-chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester. LC/MS: t_R = 1.39 min., (MH^+) = 368.16.

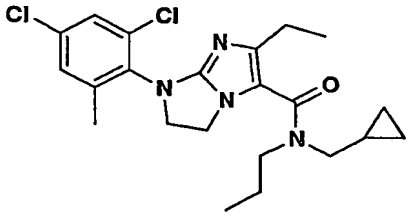
Example 30



7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for 7-(2-chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide. LC/MS: t_R = 1.46 min., (MH^+) = 475.19.

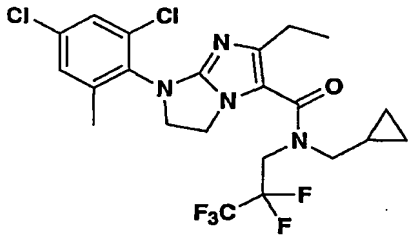
Example 31



7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.42 min., (MH^+) = 435.18.

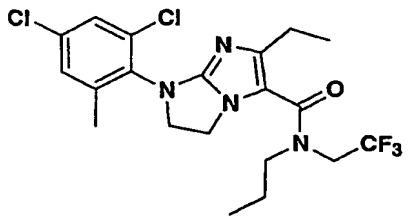
Example 32



7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,3,3,3-pentafluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.50 min., (MH^+) = 525.13.

Example 33

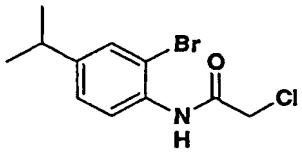


7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid propyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.41 min., (MH^+) = 463.19.

The following **Intermediates 18-23** may be used to synthesize **Examples 34-40**.

Intermediate 18

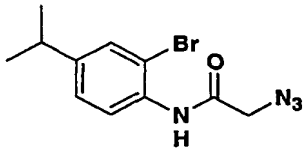


N-(2-Bromo-4-isopropyl-phenyl)-2-chloro-acetamide, scheme 3: (K)

Prepared as described for 2-chloro-N-(2,4-dichloro-6-methyl-phenyl)-acetamide.

Mass spec.: 291.97 (MH^+).

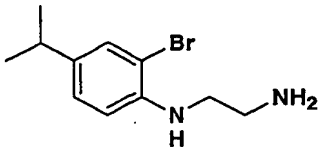
Intermediate 19



2-Azido-N-(2-bromo-4-isopropyl-phenyl)-acetamide, scheme 3: (L)

Prepared as described for 2-azido-N-(2,4-dichloro-6-methyl-phenyl)-acetamide.

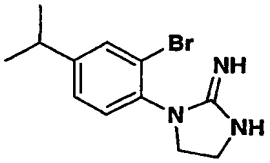
Intermediate 20



N^1-(2-Bromo-4-isopropyl-phenyl)-ethane-1,2-diamine, scheme 3: (M)

Prepared as described for N^1-(2,4-dichloro-6-methyl-phenyl)-ethane-1,2-diamine. Mass spec.: 270.08 (MH^+).

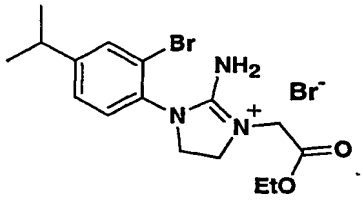
Intermediate 21



1-(2-Bromo-4-isopropyl-phenyl)-imidazolidin-2-ylideneamine, scheme 3: (N)

Prepared as described for 1-(2,4-dichloro-6-methyl-phenyl)-imidazolidin-2-ylideneamine. Mass spec.: 284.09 (MH^+).

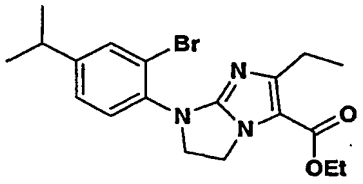
Intermediate 22



2-Amino-3-(2-bromo-4-isopropyl-phenyl)-1-ethoxycarbonylmethyl-4,5-dihydro-3H-imidazol-1-ium; bromide, scheme 3: (O)

Prepared as described for 3-ethoxycarbonylmethyl-1-(2,4-chloro-6-methyl-phenyl)-2-aminoimidazolium bromide. LC/MS: t_R = 1.29 min., (MH^+) = 368.20.

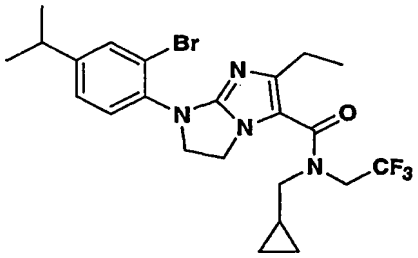
Intermediate 23



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester, scheme 3: (P)

Prepared as described for 7-(2,4-dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester. LC/MS: t_R = 1.46 min., (MH^+) = 408.23.

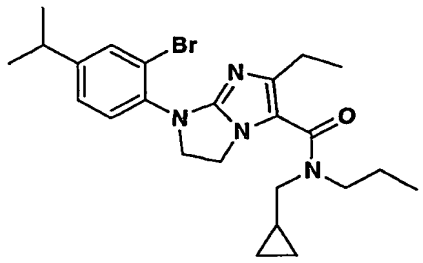
Example 34



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for 7-(2,4-dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide. LC/MS: t_R = 1.58 min., (MH^+) = 513.15.

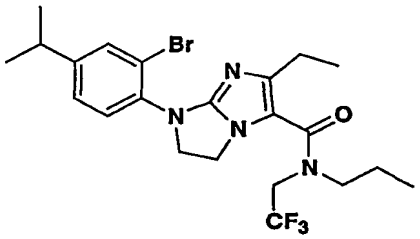
Example 35



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.47 min., (MH^+) = 473.21.

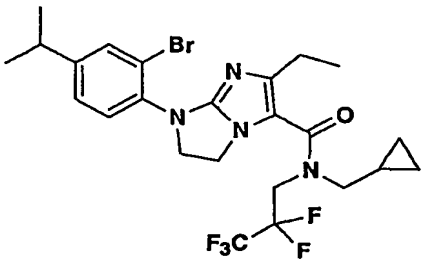
Example 36



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid propyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.47 min., (MH^+) = 501.02.

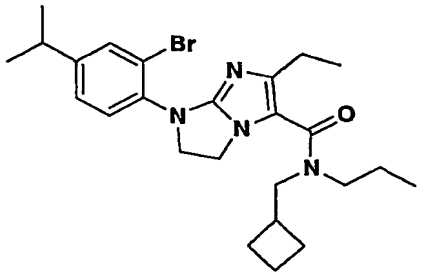
Example 37



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,3,3,3-pentafluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.61 min., (MH^+) = 564.29.

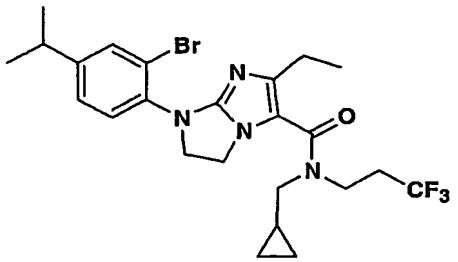
Example 38



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclobutylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.56 min., (MH^+) = 487.21.

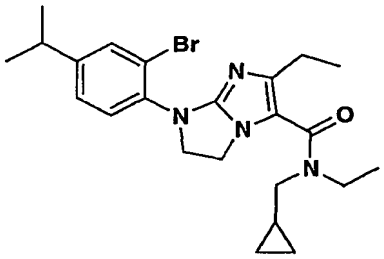
Example 39



7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.51 min., (MH^+) = 527.15.

Example 40

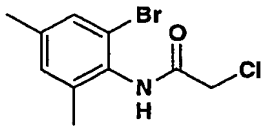


7-(2-Bromo-4-isopropyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-ethyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.43 min., (MH^+) = 459.18.

The following **Intermediates 24-29** may be used to synthesize **Examples 41-49.**

Intermediate 24

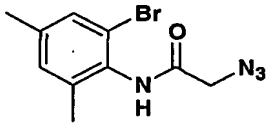


N-(2-bromo-4,6-dimethyl-phenyl)-2-chloro-acetamide, scheme 3: (K)

Prepared as described for 2-chloro-N-(2,4-dichloro-6-methyl-phenyl)-acetamide.

Mass spec.: 277.95 (MH^+).

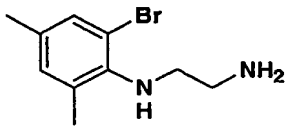
Intermediate 25



2-Azido-N-(2-bromo-4,6-dimethyl-phenyl)-acetamide, scheme 3: (L)

Prepared as described for 2-azido-N-(2,4-dichloro-6-methyl-phenyl)-acetamide.

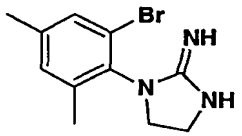
Intermediate 26



N^1-(2-bromo-4,6-dimethyl-phenyl)-ethane-1,2-diamine, scheme 3: (M)

Prepared as described for N^1-(2,4-dichloro-6-methyl-phenyl)-ethane-1,2-diamine. ^1H NMR δ ($CDCl_3$, 300 MHz) 2.22 (s, 3H), 2.31 (s, 3H), 2.87 (t, 2H), 3.04 (t, 2H), 6.88 (d, 1H), 7.17 (d, 1H). Mass spec.: 245.11 (MH^+).

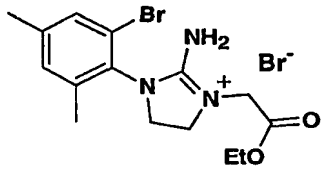
Intermediate 27



1-(2-Bromo-4,6-dimethyl-phenyl)-imidazolidin-2-ylideneamine, scheme 3: (N)

Prepared as described for 1-(2,4-dichloro-6-methyl-phenyl)-imidazolidin-2-ylideneamine. LC/MS: t_R = 0.91 min., (MH^+) = 270.08.

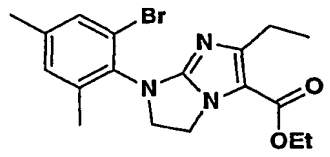
Intermediate 28



2-Amino-3-(2-bromo-4,6-dimethyl-phenyl)-1-ethoxycarbonylmethyl-4,5-dihydro-3H-imidazol-1-ium bromide, scheme 3: (O)

Prepared as described for 3-ethoxycarbonylmethyl-1-(2,4-chloro-6-methyl-phenyl)-2-aminoimidazolium bromide. LC/MS: t_R = 1.03 min., (MH^+) = 356.26.

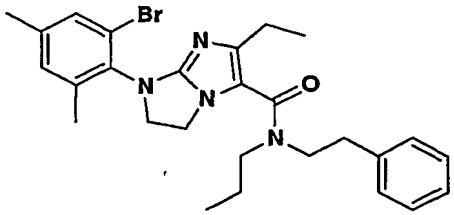
Intermediate 29



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester, scheme 3: (P)

Prepared as described for 7-(2,4-dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester. LC/MS: t_R = 1.33 min., (MH^+) = 394.31.

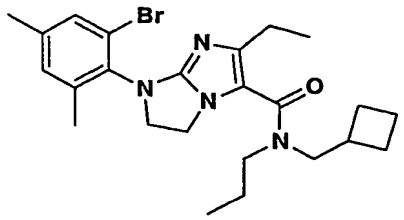
Example 41



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid phenethyl-propyl-amide, scheme 3: (Q)

Prepared as described for 7-(2,4-dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide. LC/MS: t_R = 1.42 min., (MH^+) = 511.35.

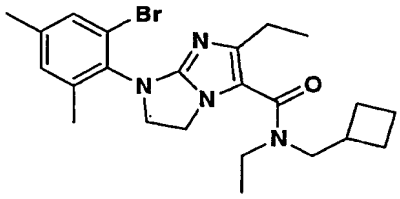
Example 42



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H imidazo[1,2-a]imidazole-3-carboxylic acid cyclobutylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.68 min., (MH^+) = 475.21.

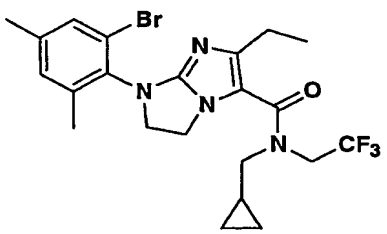
Example 43



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclobutylmethyl-ethyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.58 min., (MH^+) = 461.35.

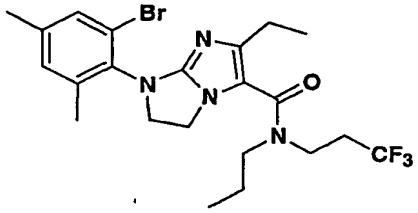
Example 44



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.28 min., (MH^+) = 501.16.

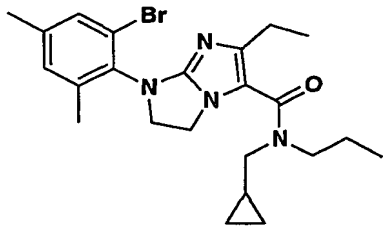
Example 45



7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid propyl-(3,3,3-trifluoro-propyl)-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.60 min., (MH^+) = 503.15.

Example 46

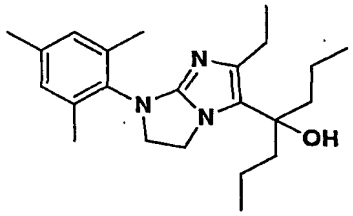


7-(2-Bromo-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 3: (Q)

Prepared as described for the example above. LC/MS: t_R = 1.56 min., (MH^+) = 461.37.

The following examples **47-48** were prepared from **Intermediate 5.**

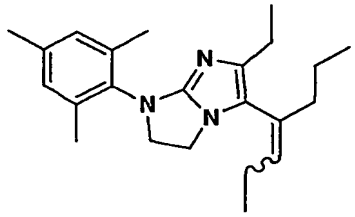
Example 47



4-[2-Ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol, scheme 11: (DDD)

To a 0°C solution of 2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazole-3-carboxylic acid ethyl ester (1 mL of a 0.14M solution in toluene) in tetrahydrofuran (1 mL) was added n-propylmagnesium chloride (0.84 mL of 1.0M in tetrahydrofuran). The resulting solution was removed from the ice bath and allowed to stir for 15 min. It was then heated at reflux for 14h. Upon cooling to room temperature, the reaction solution was quenched with saturated aqueous ammonium chloride, and the phases were separated. The aqueous phase was extracted twice with ether, and the combined organic portions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow semi-solid (0.0448 g, 86%). LC/MS: t_R = 1.58 min., (MH^+) = 370.31.

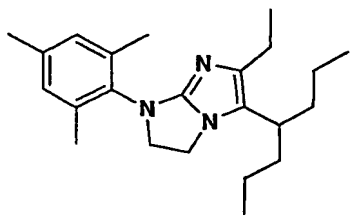
Example 48



6-Ethyl-5-(1-propyl-but-1-enyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole scheme 11: (EEE)

A mixture of 4-[2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol (0.0444 g, 0.000120 mol) and p-toluenesulfonic acid-H_2O (15 mole %) in toluene (3 mL) was heated at reflux for 1h. Upon cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue was partitioned between ether and saturated aqueous sodium bicarbonate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give the desired product in quantitative yield. LC-MS indicated the presence of two regioisomers in an approximate ratio of 2:1. LC/MS: t_R = 1.52 min. and 1.63 min., (MH^+) = 352.28.

Example 49

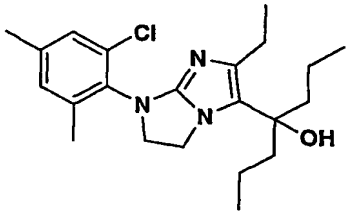


6-Ethyl-5-(1-propyl-butyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole, scheme 11: (FFF)

6-Ethyl-5-(1-propyl-but-1-enyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole (0.013 g, 0.000037 mol) in anhydrous tetrahydrofuran was treated with cold BH_3-THF (0.15 mL 1.0M in tetrahydrofuran), and the mixture was heated at reflux for 1.5 h. The mixture was cooled to 0°C, treated with glacial acetic acid (0.25 mL), heated at reflux for 1.5 h, re-cooled to 0°C, treated with 1.5 mL methanol, and heated again at reflux for 1h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between 2.5 N NaOH and ether. The organic phase was washed with water and brine, and was then dried over anhydrous Na_2SO_4 and evaporated to give a pale yellow oil. The crude product was chromatographed on silica, eluting with 15% ethyl acetate /hexanes to give a glassy solid. LC/MS: t_R = 1.81 min., (MH^+) = 354.30.

The following examples **50-51** were prepared from **Intermediates 11** and **30.**

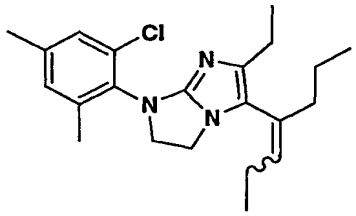
Intermediate 30



4-[7-(2-Chloro-4,6-dimethyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol, scheme 11: (DDD)

Prepared as described for 4-[2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol. The crude product was chromatographed on silica, eluting with 25% ethyl acetate/hexanes to afford only one of the possible elimination products. ^{1}H NMR δ ($CDCl_3$, 300 MHz) 7.12 (s, 1H), 7.03 (s, 1H), 5.59-5.34 (t, 1H), 4.33-4.08 (br m, 4H), 2.57-2.38 (q, 2H), 2.33 (s, 3H), 2.26(s, 3H), 2.22-2.15 (t, 2H), 1.74-1.48 (br m, 2H), 1.40-1.33 (q, 2H), 1.25-1.2 (t, 3H), 1.08-1.03 (t, 3H), 0.92-0.88 (t, 3H). LC/MS: t_R = 1.74 min., (MH^+) = 390.25.

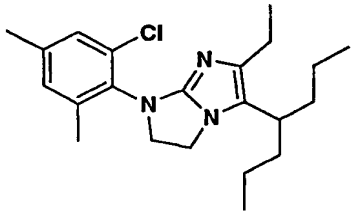
Example 50



1-(2-Chloro-4,6-dimethyl-phenyl)-6-ethyl-5-(1-propyl-but-1-enyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole, scheme 11: (EEE)

Prepared as described for 6-ethyl-5-(1-propyl-but-1-enyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole. LC/MS: t_R = 1.74 min., (MH^+) = 372.25.

Example 51

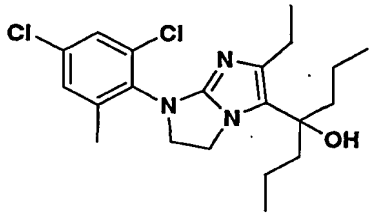


1-(2-Chloro-4,6-dimethyl-phenyl)-6-ethyl-5-(1-propyl-butyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole, scheme 11: (FFF)

Prepared as described for 6-ethyl-5-(1-propyl-butyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole. LC/MS: t_R = 1.74 min., (MH^+) = 374.21.

The following **Intermediates 17** and **31** were used to prepare **Examples 52 and 53.**

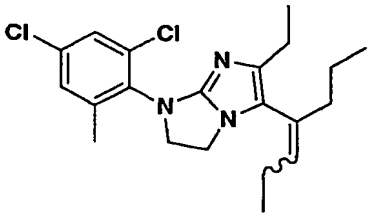
Intermediate 31



4-[7-(2,4-Dichloro-6-methyl-phenyl)-2-ethyl-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol, scheme 11: (DDD)

Prepared as described for 4-[2-ethyl-7-(2,4,6-trimethyl-phenyl)-6,7-dihydro-5H-imidazo[1,2-a]imidazol-3-yl]-heptan-4-ol. LC/MS: t_R = 1.74 min., (MH^+) = 410.17.

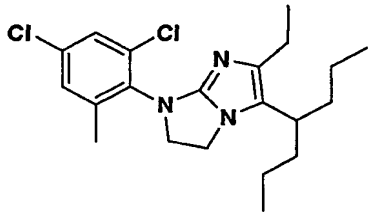
Example 52



1-(2,4-Dichloro-6-methyl-phenyl)-6-ethyl-5-(1-propyl-but-1-enyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole, scheme 11: (EEE)

Prepared as described for 6-ethyl-5-(1-propyl-but-1-enyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole. LC/MS: t_R = 1.54 min. and 1.65 min., (MH^+) = 392.18.

Example 53

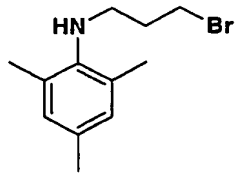


1-(2,4-Dichloro-6-methyl-phenyl)-6-ethyl-5-(1-propyl-butyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole, scheme 11: (FFF)

Prepared as described for 6-ethyl-5-(1-propyl-butyl)-1-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole. LC/MS: t_R = 1.68 min., (MH^+) = 394.10.

The following **Intermediates 32-43** may be used to synthesize **Examples 54-55**.

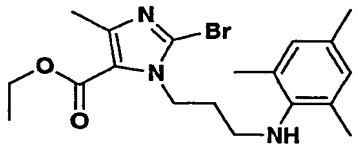
Intermediate 32



(3-Bromo-propyl)-(2,4,6-trimethyl-phenyl)-amine, scheme 7: (FF)

To a stirred ice-cold solution of 2,4,6-trimethylaniline (13.5 g, 100 mmol) in dioxane (50 mL) under argon was added 1.2 equivalents of 1.6 M n-BuLi in hexane drop-wise. The brown mixture was allowed to warm up to room temperature during 1 h. At the end 50 mL (approx. 5 equiv.) of 1,3-dibromopropane was added in one lot and stirred for 42 h. Precipitated LiBr was filtered and the volatiles were removed in vacuo. The residue was partitioned between ethyl acetate (300 mL) and water (3x100 mL). The organic layer was dried (Na_2SO_4) and evaporated to give the crude product whose purity by LC-MS analysis was 61%. Silica gel chromatography of the crude product with acetone/hexane (1:9) as eluent gave pure bromopropyl aniline (3.3 g) and an impure fraction which upon crystallization from ethyl acetate hexane gave an additional 2.4 g. (22 % yield). LC/MS: t_R = 1.2 min; [M + H] = 256, 258 (bromine pattern), ^{1}H NMR (CD_3OD) δ 7.07 (2 H, s), 3.59 (2 H, t, J_{vic} = 6.4 Hz), 3.51 (2 H, t, J_{vic} = 8.1 Hz), 2.46 (6 H, s), 2.45 - 2.38 (2 H, m), 2.30 (3 H, s).

Intermediate 33

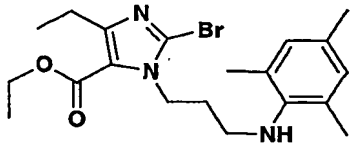


2-Bromo-5-methyl-3-[3-(2,4,6-trimethyl-phenylamino)-propyl]-3H-imidazole-4-carboxylic acid ethyl ester, scheme 7: GG)

A solution of (1.26 g, 5.4 mmol) bromoimidazole in acetone (43 mL) was combined with (3-bromopropyl)-2,4,6-trimethylaniline (1.1g, 4.25 mmol) and diazabicycloundecene (1.2 equiv). After 96 h, acetone was evaporated and the residue was partitioned between ethyl acetate (250 mL) and water (3 x 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by silica

gel column chromatography using a step gradient of 0% to 70% ethyl acetate in hexane to give 1.1 g (50 % yield) of the required alkylated product. t_R = 1.3 min., MS: [M+H] = 408, 410 (bromine pattern), ^{1}H NMR ($CDCl_3$) δ 6.82 (2 H, s), 4.45 (2 H, t, J_{vic} = 7.5 Hz), 4.32 (2 H, q, J_{vic} = 7.1 Hz), 3.05 (2 H, t, J_{vic} = 7.0 Hz), 2.46 (3 H, s), 2.29 (6 H, s), 2.29 (3 H, s), 2.05 (2 H, m), 1.37 (3 H, t, J_{vic} = 7.1 Hz). ^{13}CNMR ($CDCl_3$) δ 160.3, 148.7, 129.7, 124.7, 121.1, 60.6, 46.0, 45.7, 20.6, 18.5, 16.1, 14.3. A more polar product (0.04g) which corresponded to cyclization product from the N-3 alkylation of imidazole was also obtained from the later fractions.

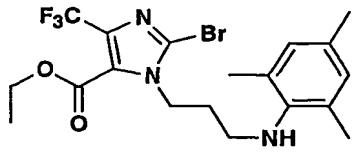
Intermediate 34



2-Bromo-5-ethyl-3-[3-(2,4,6-trimethyl-phenylamino)-propyl]-3H-imidazole-4-carboxylic acid ethyl ester, scheme 7: (GG)

This compound was prepared from the corresponding 2-bromoimidazole on a 12.9 mmol scale as described in the previous example. Silica gel chromatography of the crude product using a step gradient of 20-70 % ethyl acetate in hexane provided N3-derived cyclization product (0.47g, 11 % yield), t_R = 1.3 min., MS: [M+H] = 342, and N1-derived alkylation product (2.9g, 54 % yield); LC/MS: t_R = 1.5 min., [M+H] = 422, 424 (bromine pattern), ^{1}H NMR (CD_3OD) δ 6.74 (2 H, s), 4.40 (2 H, t, J_{vic} = 7.6 Hz), 4.31 (2 H, q, J_{vic} = 7.2 Hz), 2.94 (2 H, t, J_{vic} = 7.1 Hz), 2.83 (2 H, q, J_{vic} = 7.6 Hz), 2.19 (6 H, s), 2.16 (3 H, s), 1.93 (2 H, m), 1.34 (3 H, t, J_{vic} = 7.2 Hz), 1.19 (3 H, t, J_{vic} = 7.6 Hz). ^{13}CNMR (CD_3OD) δ 161.2, 154.8, 144.0, 132.7, 130.9, 130.5, 126.2, 121.8, 62.0, 47.10, 46.59, 32.2, 23.70, 20.8, 18.7, 14.6, 14.5, 14.3.

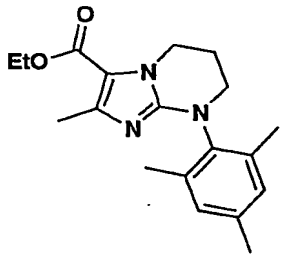
Intermediate 35



2-Bromo-5-trifluoromethyl-3-[3-(2,4,6-trimethyl-phenylamino)-propyl]-3H-imidazole-4-carboxylic acid ethyl ester, scheme 7: (GG)

To a 0.1M dimethylformamide solution containing 5.3 mmol each of the bromoimidazole and bromopropyl aniline was added 1.2 equivalents of Cs_2CO_3. The reaction mixture was stirred at ambient temperature for 96 h. LC-MS indicated approximately 50% conversion to a single alkylated product. Diluted with ethyl acetate (500 mL) and washed with water (3 x 100 mL). Approx. 5 mL ethanol had to be used to break up an emulsion. The ethyl acetate layer was dried (Na_2SO_4), evaporated in vacuo. The crude product was purified by silica gel chromatography with ethyl acetate:hexane (1:9) as eluent. Fractions containing the required compound were combined and evaporated to give 0.51g (21 % yield). LC/MS: t_R = 1.5 min., [M+H] = 462, 464 (bromine pattern), ^{1}H NMR (CD_3OD) δ 6.74 (2 H, s), 4.44 (2 H, t, J_{vic} = 7.5 Hz), 4.35 (2 H, t, J_{vic} = 7.1 Hz), 2.96 (2 H, t, J_{vic} = 7.1 Hz), 2.20 (6 H, s), 2.15 (3H, s), 1.97 (2 H, m), 1.33 (3 H, t, J_{vic} = 7.1 Hz).

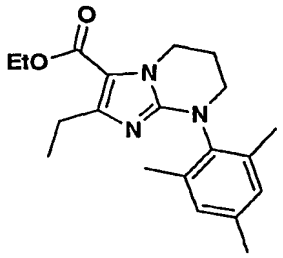
Intermediate 36



2-Methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester, scheme 7: (HH)

The appropriate N1-alkylated 2-bromoimidazole (1 g, 2.1 mmol) in sulfolane (50 mL) was heated under argon in the dark with 1.2 equivalents of Ag_2CO_3 for 24h. The reaction mixture was cooled to ambient temperature. Filtered, diluted with water containing 0.1% trifluoroacetic acid to 250 mL. The dark filtrate was applied to an octadecyl silica gel (C18) column (4 x 15 cm) pre-equilibrated with water containing 0.1 % trifluoroacetic acid. Elution with the same solvent was continued until all the sulfolane was removed. The solvent was then changed to methanol:0.1 % trifluoroacetic acid in water (2:3) collecting 25 mL size fractions which were combined after LC-MS analysis to give 0.9 g of the required product as trifluoroacetate salt of 93 % purity. LC/MS: t_R = 1.1 min., [M+H] = 328, ^{1}H NMR (CD_3OD) δ 6.94 (2 H, s), 4.29 - 4.24 (4 H, m), 3.47 (2 H, t, J_{vic} = 5.5 Hz), 2.27 (3 H, s), 2.25 (3 H, s), 2.29 (3 H, s), 2.24 (2 H, m), 2.12 (6 H, s), 1.34 (3 H, t, J_{vic} = 7.0 Hz). ^{13}CNMR (CD_3OD) δ 162.7, 150.3, 147.9, 139.1, 138.8, 137.8, 130.7, 115.2, 60.8, 47.6, 44.4, 23.2, 21.2, 18.3, 15.2, 14.9.

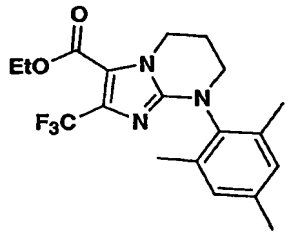
Intermediate 37



2-Ethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester, scheme 7: (HH)

To the N1-alkylated 2-bromo-4-ethyl imidazole derivative (2.83 g, 6.7 mmol) in sulfolane (67 mL) was added 1.1 equivalents of silver triflate. The resulting solution was stirred in the dark at 150°C under argon. Within 10 min the solution turned dark and it was stirred for 24 h when LC-MS indicated complete conversion to cyclized product. The reaction mixture was cooled to ambient temperature. Filtered, diluted with water containing 0.1% trifluoroacetic acid to 335 mL and filtered again. The dark filtrate was applied to an octadecyl silica gel (C18) column (4 x 15 cm) pre-equilibrated with water containing 0.1 % trifluoroacetic acid. Elution with the same solvent was continued until all the sulfolane was removed. The solvent was then changed to methanol:0.1 % trifluoroacetic acid in water (2:3) collecting 25 mL size fractions which were combined after LC-MS analysis to give two major fractions. Cyclization product that was 84 % pure (1.5 g) and pure cyclization product (570 mg). LC/MS: t_R = 1.3 min., [M+H] = 342,

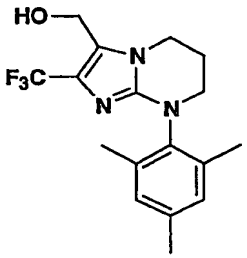
Intermediate 38



2-Trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2a] pyrimidine-3-carboxylic acid ethyl ester, scheme 7: (HH)

The appropriate N1-alkylated-2-bromoimidazole (0.473g, 1.02 mmol) was subjected to silver triflate mediated cyclization in sulfolane (10 mL) as described above except that the reaction was carried out for 48 h. At the end, the mixture was diluted with ethanol (10 mL) filtered through a bed (2 x 4.5 cm) of C18 silica gel and washed with another 50 mL more ethanol. The filtrate was concentrated in vacuo to ca. 20 mL. It was then purified by preparative HPLC using a 20 min. linear gradient (25 min run) of 30-100 % B in A in ten injections. Fractions containing the cyclization product were combined and evaporated. The residue (0.39g) in 20 mL anhydrous ethanol was stirred with (0.168 g, 2 mmol) $NaHCO_3$ for 1.5 h. Filtered and evaporated to dryness to give 0.23 g (60 % yield) of cyclized product. LC/MS: t_R = 1.8 min., [M+H] = 382.

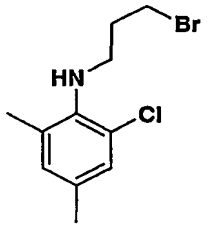
Intermediate 39



[2-Trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-yl]-methanol, scheme 7: (II)

The appropriate ethyl ester (0.032g) in 1 mL of anhydrous tetrahydrofuran was treated with an excess (0.3 mL) of 1 M $LiAlH_4$ in tetrahydrofuran at ambient temperature. After 1h, 1 M NaOH (5 mL) was carefully added. Most of the tetrahydrofuran was then evaporated. The residue was partitioned between ethyl acetate (2 x 30 mL) and additional 10 mL 1 M NaOH. Organic layer was dried (Na_2SO_4) and evaporated. The residue after silica gel chromatography with methanol:methylene chloride (1:99) yielded (0.025g) of alcohol. LC/MS: t_R = 1.0 min., [M+H] = 340, ^{1}H NMR (CD_3OD) δ 6.93 (2 H, s), 4.62 (2 H, s), 4.10 (2 H, t, J_{vic} = 6.1 Hz), 3.51 (2 H, t, J_{vic} = 5.4 Hz), 2.29 (2 H, m), 2.27 (3H, s), 2.13 (6 H, s). Gradient NOESY experiment revealed NOE between exo methylene group and the methylene at 6 position confirming the regiochemistry.

Intermediate 40

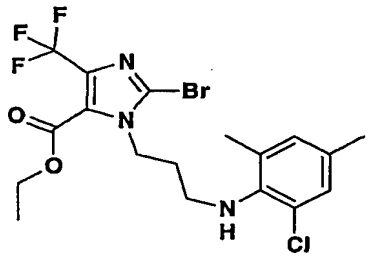


(3-Bromo-propyl)-(2-chloro-4,6-dimethyl-phenyl)-amine, scheme 7: FF)

To a solution of the 2-chloro-4,6-dimethyl aniline (16.9g g, 108 mmol) in 1,4-dioxane (80 mL) was added n-butyl lithium solution (2.5 M in hexanes, 48 mL), dropwise, at 0°C under argon. The reaction mixture was warmed up to rt and stirred for 20 min. 1,3-Dibromopropane (109 g, 543 mmol) was added and the reaction mixture was stirred overnight. The mixture was filtered through celite and

concentrated. Purification was carried out by reverse phase chromatography using water, methanol and trifluoroacetic acid to obtain product (20.01 g, 72.5 mmol, 67%) as brown oil. LC/MS: t_R = 1.5 min. [M+H] 277. ^{1}H NMR (CD_3OD) δ: 7.12 (s, 1H), 6.99 (s, 1H), 3.52 (t, J = 6.65 Hz, 2H), 3.36 (t, J = 6.75 Hz, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 2.14 (m, 2H).

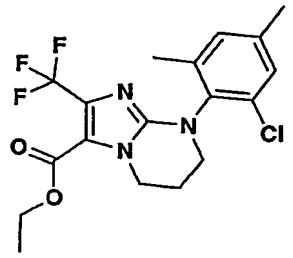
Intermediate 41



2-Bromo-3-[3-(2-chloro-4,6-dimethyl-phenylamino)-propyl]-5-trifluoromethyl-3H-imidazole-4-carboxylic acid ethyl ester, scheme 7: (GG)

To a solution of the imidazole (5.08 g, 17.7 mmol) in dry dimethylformamide (120 mL) was added the 3-bromopropyl aniline (5.37 g, 19.5 mmol) and cesium carbonate (8.64 g, 26.5 mmol) at RT under argon. The reaction mixture was heated at 55°C overnight, cooled and diluted with ethyl acetate (400 mL). The organic phase was washed with water (2x), brine and dried ($MgSO_4$). Purification by silica gel column chromatography using hexanes/ethyl acetate (90:10 to 70:30) afforded product (5.98 g, 12.4 mmol, 70%) as brown oil. LC/MS: t_R = 2.2 min. [M+H] 483. ^{1}H NMR (CD_3OD) δ: 6.98 (s, 1H), 6.86 (s, 1H), 4.49 (t, J = 7.55 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.10 (t, J = 6.95 Hz, 2H), 2.25 (s, 3H), 2.19 (s, 3H), 2.00 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H).

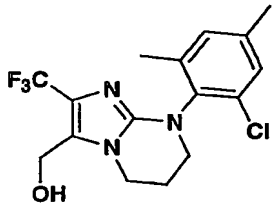
Intermediate 42



1-(2-Chloro-4,6-dimethyl-phenyl)-6-trifluoromethyl-2,3,4,4a-tetrahydro-1H-[1]pyrindine-5-carboxylic acid ethyl ester, scheme 7: HH)

To a solution of the alkylated imidazole (5.98 g, 12.4 mmol) in sulfolane (50 mL) was added silver triflate (4.77 g, 18.6 mmol) at rt under argon. The flask was fitted with a reflux condenser and heated at 150°C overnight. The whole setup was covered with aluminum foil to keep the reaction mixture in dark. The reaction mixture was filtered through celite and purified by reverse phase chromatography, using water, methanol and trifluoroacetic acid. Product (3.43 g, 8.54 mmol, 69%) was obtained as brown solid. LC/MS: t_R = 2.1 min. [M+H] 402. ^{1}H NMR (CD_3OD) δ: 7.01 (s, 1H), 6.92 (s, 1H), 4.38 (m, 2H), 4.32 (q, J = 7.15 Hz, 2H), 4.65 (m, 2H), 2.30 (m, 2H), 2.26 (s, 3H), 2.19 (s, 3H), 2.00 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H).

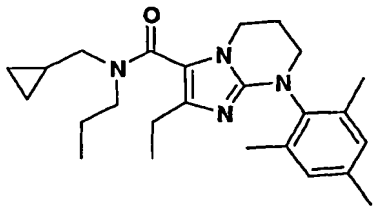
Intermediate 43



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-yl]-methanol, scheme 7: (II)

To a solution of the ester (3.43 g, 8.54 mmol) in anhydrous tetrahydrofuran (100 mL) at 0°C under argon was added dropwise a solution of Lithium aluminum hydride (1 M in hexanes, 86 mL). The reaction mixture was stirred for an hour and an aqueous solution of Rochelle salt was added dropwise to quench excess of LAH. The reaction mixture was extracted with ethyl acetate (3x100 mL). The combined organic layer was washed with water (2x), brine and dried ($MgSO_4$). Purification by silica gel column chromatography, using hexanes, ethyl acetate (90:10 to 60:40) afforded product (2.12 g, 5.89 mmol, 69%) as off white solid. LC/MS: t_R = 1.5 min. [M+H] 360. ^{1}H NMR ($CDCl_3$) δ: 7.10 (s, 1H), 6.97 (s, 1H), 4.04 (m, 2H), 3.65 (m, 2H), 3.42 (m, 2H), 2.32 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H).

Example 54

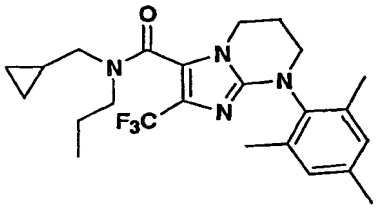


2-Ethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 7: (LL)

A solution of 0.15 g of N-cyclopropylmethyl, N-propyl amine (1.3 mmol) in toluene (5 mL) was treated with 0.47 mL of 2 M trimethylaluminum in hexanes (0.94 mmol). After 1h anhydrous toluene solution (2 mL) of the appropriate ethyl ester (59 mg, 0.17 mmol) was added. Refluxed for 4h. Allowed to cool to ambient temperature, diluted with 25 mL dichloromethane and washed with 1M NaOH (8 mL), and water (8 mL). Organic layer was evaporated and the residue in 2 mL dimethylformamide was purified by prep HPLC using a 20 min linear gradient of 30-100 % B in A in a

25 min run. Fractions containing the required compound were combined to give 11mg of the amide. LC/MS: t_R = 1.4 min., [M+H] = 409. ^{1}H NMR (CD_3OD) δ 7.10 (2 H, s), 4.20 - 3.20 (8H, 4 x m), 2.47 (2 H, m), 2.38 (2H, m), 2.33 (3 H, s), 2.23 (6 H, s), 1.80 - 1.57 (2 H, m), 1.22 - 0.20 (11 H, 4 x m). Fractions containing unchanged ethyl ester were combined to recover the starting ethyl ester (43 mg) as trifluoroacetate salt.

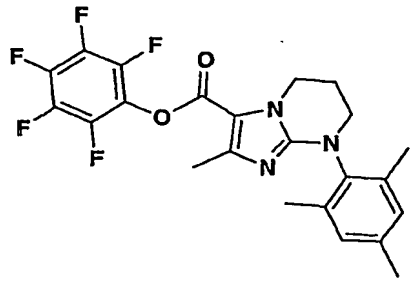
Example 55



2-Trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2 a]pyrimidine-3-carboxylic acid cyclopropylmethyl-propyl-amide, scheme 7: (LL)

The corresponding ethyl ester was subjected to Weinreb amidation using standard protocols. The amide obtained was purified by Preparative HPLC with a 15 min linear gradient of B in A in a 20 min run. Combined fractions were evaporated in vacuo to give the required product. LC/MS: t_R = 1.8 min., [M+H] = 449, ^{1}H NMR (CD_3OD) δ 7.03 (2 H, s), 4.04 - 3.97 (2H, 2 x m), 3.64 (2 H, t, J_{vic} = 5.6 Hz), 3.62 - 3.02 (4 H, 4 x m), 2.47 - 2.32 (2 H, m), 2.31 (3 H, s), 2.21 (3 H, s), 2.20 (3H, s), 1.81 - 1.07 (3 H, 3 x m), 1.06 - 0.82 (3 H, 2 x m), 0.70 - 0.02 (4 H, 3 x m).

Intermediate 44

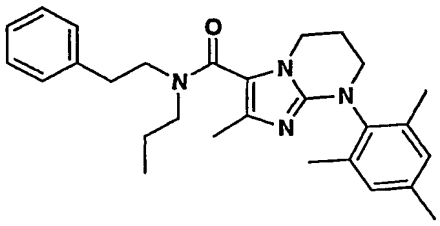


2-Methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid pentafluorophenyl ester, scheme 7: (HH)

The corresponding ethyl ester (0.17 mg, 0.52 mmol) and $LiOH-H_2O$ (110 mg) in dimethoxyethane:water (1:1, 113 mL) was heated to 55°C for 24 h. Dimethoxyethane and water were evaporated. The residue in 3 mL dimethyl formamide was treated with pentafluorophenyl trifluoroacetate (2.5 mL) and stirred for 2 h. Volatiles were evaporated and the residue was purified by silica gel column chromatography with methylene chloride and 2-propanol: methylene chloride (3:47). Fractions containing the required activated pentafluorophenyl ester were combined to give 0.15 g, 32 % yield). LC/MS: t_R = 1.5 min., [M+H] = 466.

General Procedure for amide formation **preparation of Example 56-58** from **Intermediate 44**: The pentafluorphenyl ester (15 mg, 0.036 mmol) in 1 mL dimethylformamide was stirred with 0.18 mmol of appropriate amine and 0.18 - 0.36 mmol Cs_2CO_3 at 70°C for 18 h. The mixture was diluted with water (0.8 mL) and trifluoroacetic acid (0.2 mL). The resulting solution was purified by preparative HPLC using a 20 min linear gradient with 30-100 % B in A as eluent in a 25 min run. Fractions containing the required product were combined and evaporated to give the appropriate amide in 20-50 % yield.

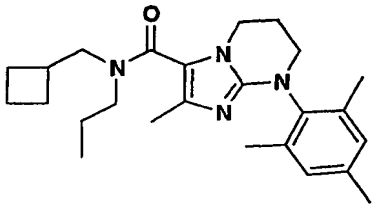
Example 56



2-Methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid phenethyl-propyl-amide, scheme 7: (LL)

Prepared as described for the example above. LC/MS: t_R = 1.3 min., [M+H] = 445, ^{1}H NMR (CD_3OD) δ 7.31 - 7.16 (5 H, m), 7.09 (2 H, s), 4.31 - 2.72 (12 H, 7 x m), 2.32 (3 H, s), 2.20 (6 H, s), 2.05 - 1.43 (5 H, m), 1.28 - 0.77 (3 H, 2 x m).

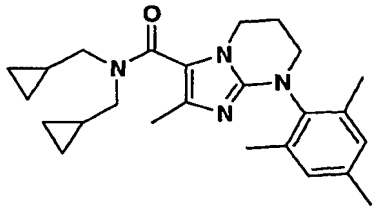
Example 57



2-Methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid cyclobutylmethyl-propyl-amide, scheme 7: (LL)

LC/MS: t_R = 1.3 min., [M+H] = 409, ^{1}H NMR (CD_3OD) δ 7.10 (2 H, s), 4.43 - 3.79 (2 H, m), 3.70 (2 H, t, J_{vic} = 5.5 Hz), 3.62 - 3.10 (4 H, m), 2.91 - 2.53 (1 H, m), 2.38 - 2.36 (2 H, m), 2.33 (3 H, s), 2.22 (6 H, s), 2.10 - 1.22 (11 H, 4 x m), 1.16 - 0.79 (3 H, m).

Example 58

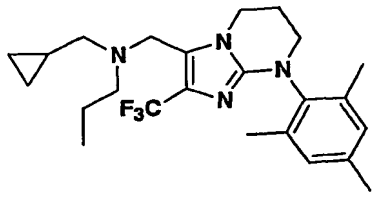


2-Methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine-3-carboxylic acid bis-cyclopropylmethyl-amide, scheme 7: (LL)

LC/MS: t_R = 1.4 min., [M+H] = 409, ^{1}H NMR (CD_3OD) δ 7.10 (2 H, s), 4.15 - 3.95 (2 H, m), 3.70 (2 H, t, J_{vic} = 5.5 Hz), 3.68 - 3.36 (4 H, m), 2.39 - 2.36 (2 H, m), 2.33 (3 H, s), 2.23 (6 H, s), 2.09 (3 H, s), 1.25 - 1.05 (4 H, m), 0.41 - 0.05 (4 H, m).

Intermediate 39 was used to prepare **Examples 59-95 and 331**.

Example 59

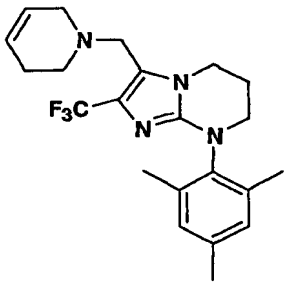


Cyclopropylmethyl-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Intermediate 39 was dissolved in benzene (50 mL) and treated with with thionyl chloride (5 mL). The solution was heated at reflux for 2h. The volatiles were evaporated. The residue was evaporated twice with heptane (50 mL). The resulting gum was dissolved in acetonitrile (30 mL) and treated with excess N-cyclopropylmethyl, N-propyl-amine (1 mL). After 1h LC-MS indicated clean

conversion to the required dialkylaminomethyl derivative. Acetonitrile was evaporated and the residue was purified by C18 column chromatography with a step gradient elution using 20-60 % methanol in water containing 0.1 % trifluoroacetic acid. Fractions containing the required product were combined and evaporated in vacuo to give the required amine (0.17g, 51 % overall yield from the cyclization product). LC/MS: t_R = 1.3 min., [M+H] = 435, ^{1}H NMR (CD_3OD) δ 6.98 (2 H, s), 4.56 (2H, s), 4.16 (2 H, t, J_{vic} = 5.8 Hz), 3.60 (2 H, t, J_{vic} = 5.5 Hz), 3.23 - 3.18 (4 H, 2 x m), 2.36 (2 H, m), 2.29 (3 H, s), 2.15 (6 H, s), 1.81 - 1.76 (2 H, m), 1.28 -1.21 (1 H, m), 1.02 (3 H, t, J_{vic} = 7.3 Hz), 0.86 - 0.82 (2 H, m), 0.51 - 0.47 (2 H, m).

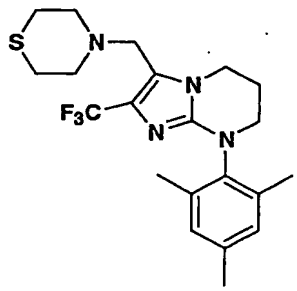
Example 60



3-(3,6-Dihydro-2H-pyridin-1-ylmethyl)-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.3 min., MS: [M+H] = 405.

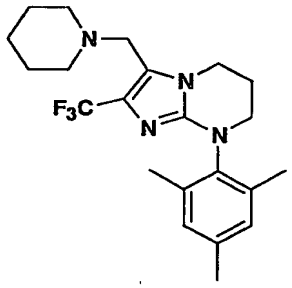
Example 61



3-Thiomorpholin-4-ylmethyl-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 425.

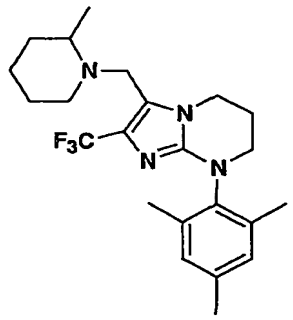
Example 62



3-Piperidin-1-ylmethyl-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 407.

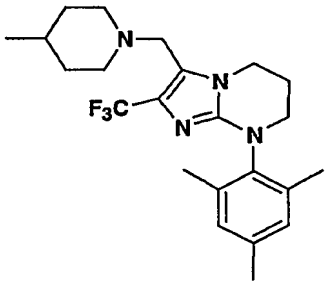
Example 63



3-(2-Methyl-piperidin-1-ylmethyl)-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min., MS: [M+H] = 421.

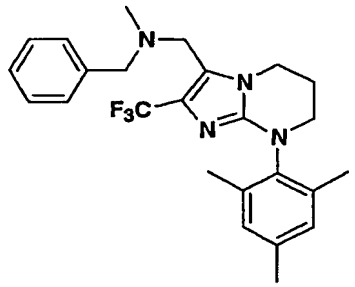
Example 64



3-(4-Methyl-piperidin-1-ylmethyl)-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 421.

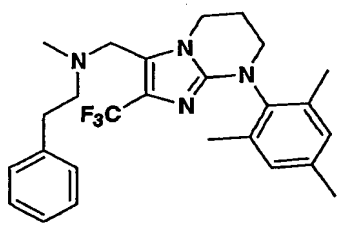
Example 65



Benzyl-methyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 443.

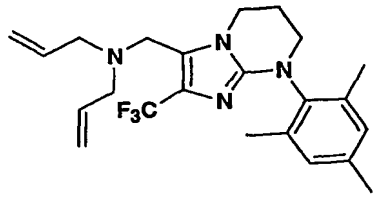
Example 66



Methyl-phenethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 457.

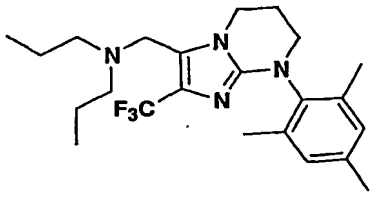
Example 67



Diallyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min., MS: [M+H] = 419.

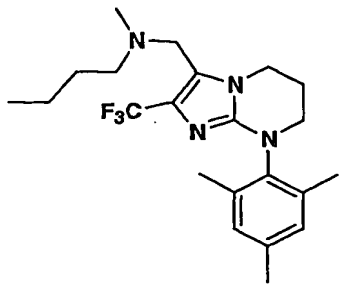
Example 68



Dipropyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min., MS: [M+H] = 423.

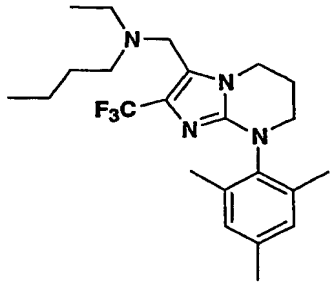
Example 69



Butyl-methyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min., MS: [M+H] = 409.

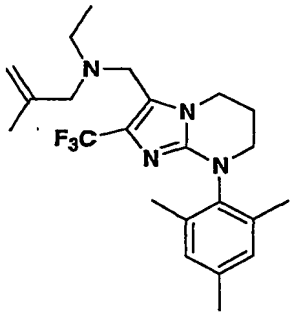
Example 70



Butyl-ethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min., MS: [M+H] = 423.

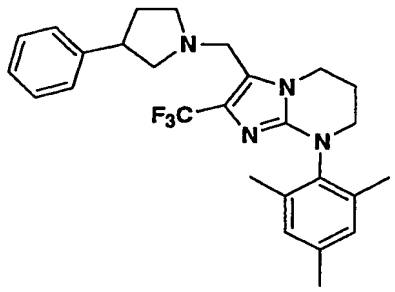
Example 71



Ethyl-(2-methyl-allyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min., MS: [M+H] = 421.

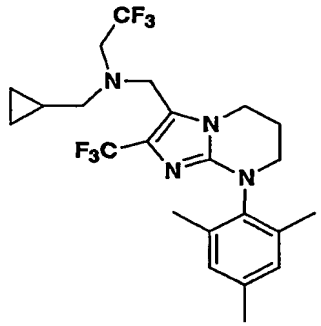
Example 72



3-(3-Phenyl-pyrrolidin-1-ylmethyl)-2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 469.

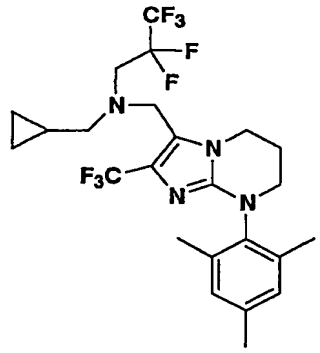
Example 73



Cyclopropylmethyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 475.

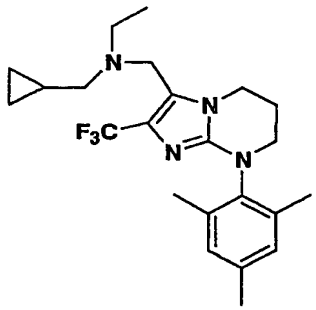
Example 74



Cyclopropylmethyl-(2,2,3,3,3-pentafluoro-propyl)-[2trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min., MS: [M+H] = 525.

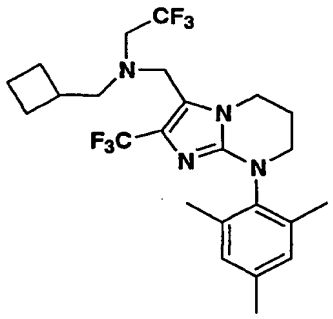
Example 75



Cyclopropylmethyl-ethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.3 min., MS: [M+H] = 421.

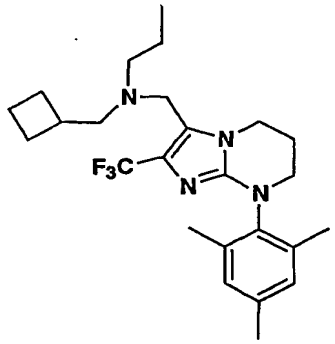
Example 76



Cyclobutylmethyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min., MS: [M+H] = 489.

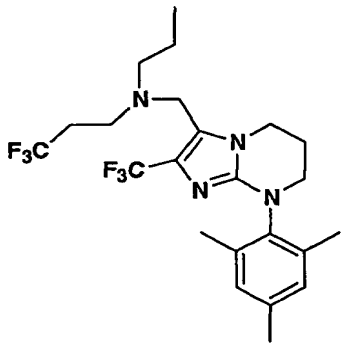
Example 77



Cyclobutylmethyl-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min., MS: [M+H] = 449.

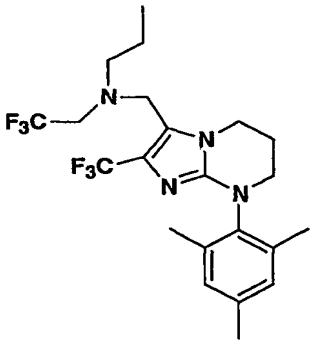
Example 78



Propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 477.

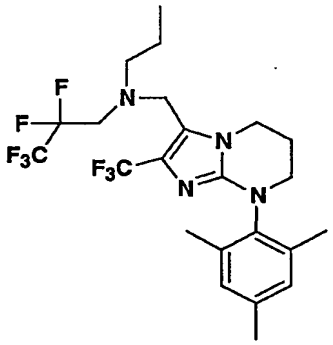
Example 79



Propyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min., MS: [M+H] = 463.

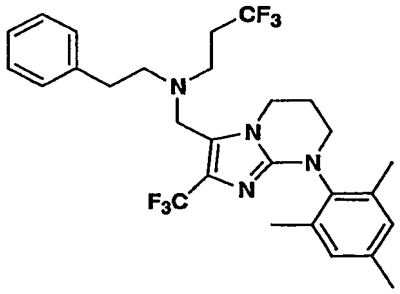
Example 80



(2,2,3,3,3-Pentafluoro-propyl)-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 2.0 min., MS: [M+H] = 513.

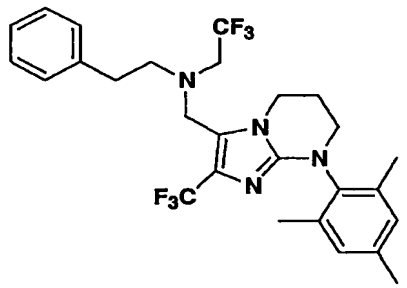
Example 81



Phenethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 2.0 min., MS: [M+H] = 539.

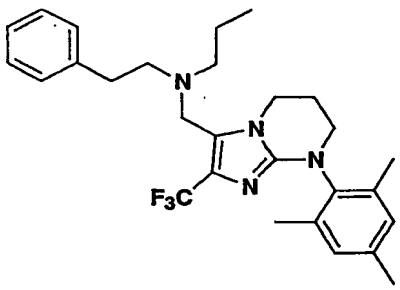
Example 82



Phenethyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min., MS: [M+H] = 525.

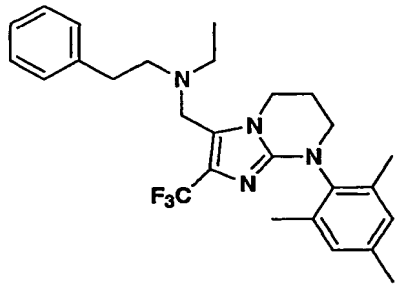
Example 83



Phenethyl-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 485.

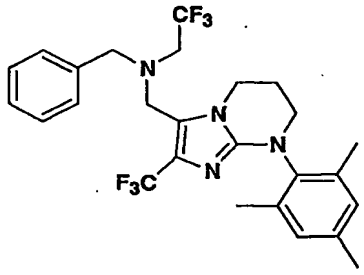
Example 84



Ethyl-phenethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min., MS: [M+H] = 471.

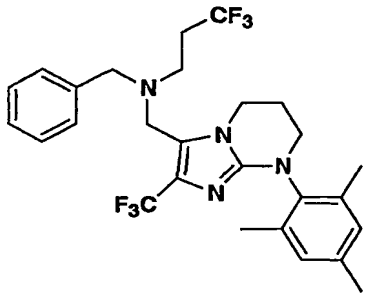
Example 85



Benzyl-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 511.

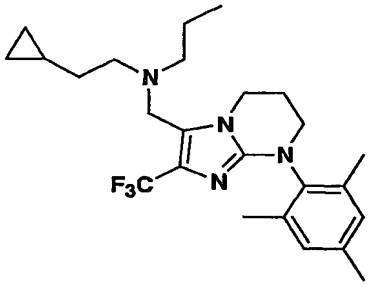
Example 86



Benzyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 525.

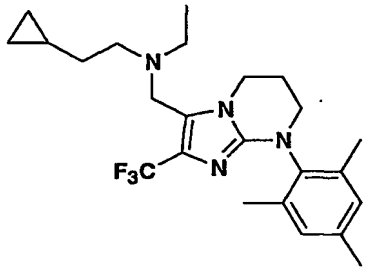
Example 87



(2-Cyclopropyl-ethyl)-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min., MS: [M+H] = 449.

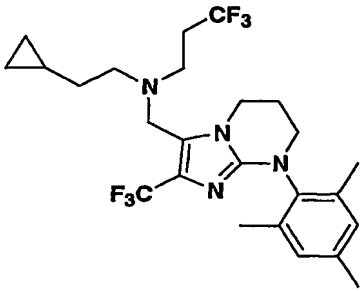
Example 88



(2-Cyclopropyl-ethyl)-ethyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 435.

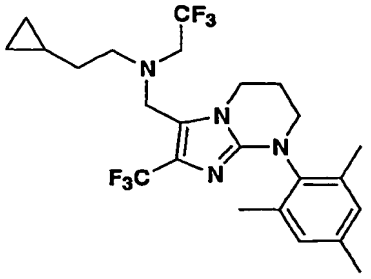
Example 89



(2-Cyclopropyl-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 2.0 min., MS: [M+H] = 503.

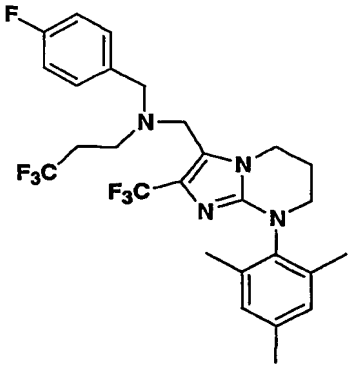
Example 90



(2-Cyclopropyl-ethyl)-(2,2,2-trifluoro-ethyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 489.

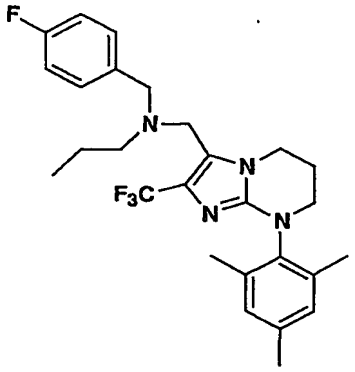
Example 91



(4-Fluoro-benzyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 543.

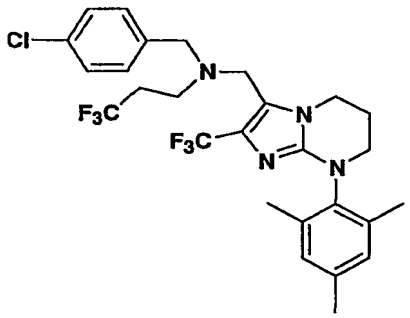
Example 92



(4-Fluoro-benzyl)-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min., MS: [M+H] = 489.

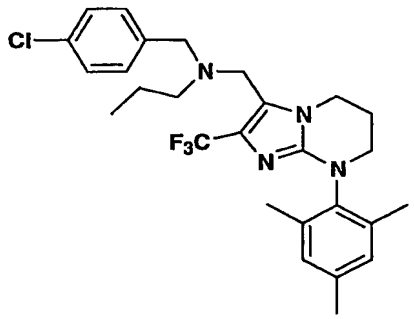
Example 93



(4-Chloro-benzyl)-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min., MS: [M+H] = 559.

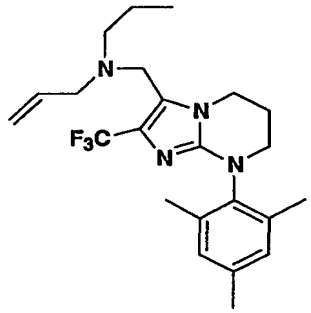
Example 94



(4-Chloro-benzyl)-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min., MS: [M+H] = 505.

Example 95

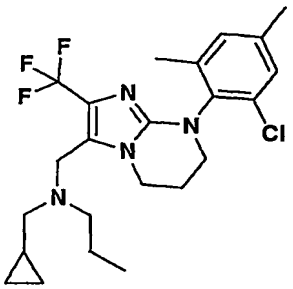


Allyl-propyl-[2-trifluoromethyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min., MS: [M+H] = 421.

Intermediate 43 was used to prepare **Examples 96-138**.

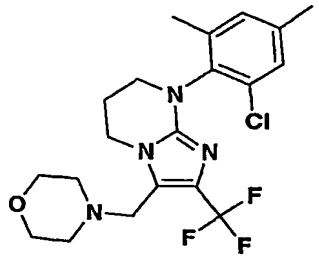
Example 96



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclopropylmethyl-propyl-amine, scheme 7: (KK)

To a solution of the appropriate alcohol (0.092 mg, 0.25 mmol) in benzene (20 mL) was added thionyl chloride (0.15 g, 1.28 mmol) at 0°C, under argon. The reaction mixture was stirred for an hour the solvent was removed on a rotary evaporator. Traces of thionyl chloride were removed by co-evaporating with dichloromethane 3 times. The residue was dissolved in dichloromethane (50 mL) and to that solution was added the N-propyl-cyclopropylmethylamine (0.058 g, 0.512 mmol) and diisopropylethyl amine (0.099 g, 0.768 mmol) at rt. The reaction mixture was stirred overnight. Solvent was concentrated, the residue dissolved in methanol (2 mL) and purification carried out by reverse phase preparative HPLC using water, methanol, trifluoroacetic acid to obtain the product (0.084 g, 0.15 mmol, 70%) as colorless oil. LC/MS: t_R = 1.4 min. [M+H] 455. ^{1}H NMR (CD_3OD) δ: 7.20 (s, 1H), 7.11 (s, 1H), 4.58 (m, 2H), 4.19 (m, 2H), 3.68 (m, 1H), 3.59 (m, 1H), 3.23 (m, 4H), 2.39 (m, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 1.79 (m, 2H), 1.22 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H0, 0.83 (m, 2H), 0.50 (m, 2H).

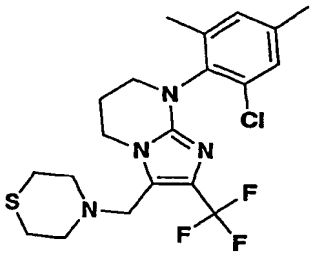
Example 97



8-(2-Chloro-4,6-dimethyl-phenyl)-3-morpholin-4-ylmethyl-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.3 min. [M+H] 429.

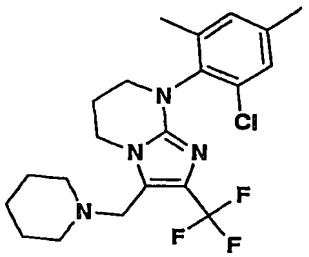
Example 98



8-(2-Chloro-4,6-dimethyl-phenyl)-3-thiomorpholin-4-ylmethyl-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.3 min. [M+H] 445.

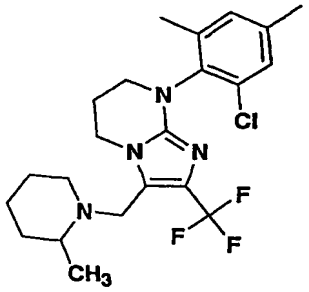
Example 99



8-(2-Chloro-4,6-dimethyl-phenyl)-3-piperidin-1-ylmethyl-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 427.

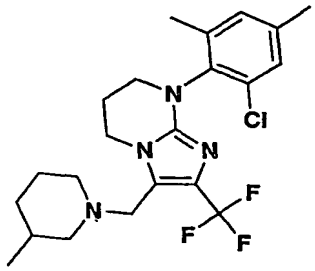
Example 100



8-(2-Chloro-4,6-dimethyl-phenyl)-3-(2-methyl-piperidin-1-ylmethyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

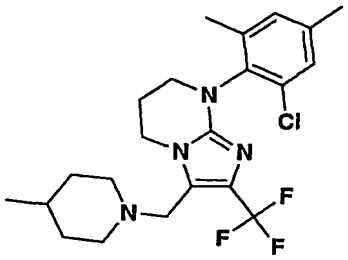
Example 101



8-(2-Chloro-4,6-dimethyl-phenyl)-3-(3-methyl-piperidin-1-ylmethyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

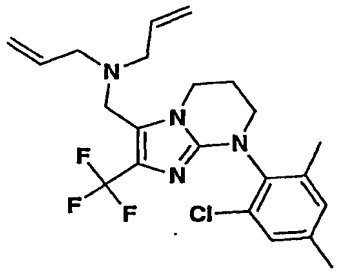
Example 102



8-(2-Chloro-4,6-dimethyl-phenyl)-3-(4-methyl-piperidin-1-ylmethyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

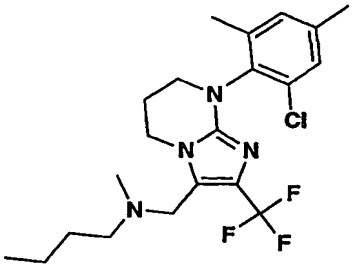
Example 103



Diallyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 439.

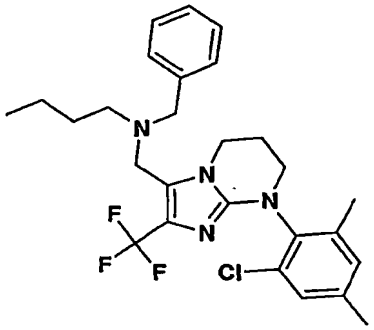
Example 104



Butyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-methyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 429.

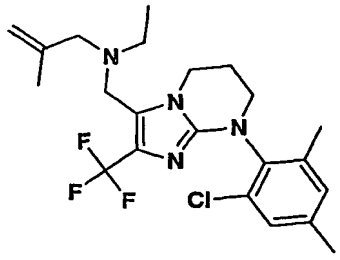
Example 105



Benzyl-butyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min. [M+H] 506.

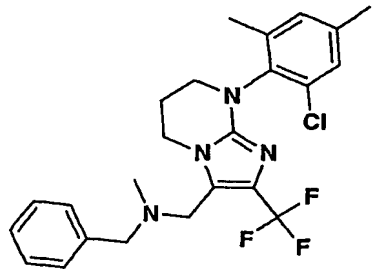
Example 106



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-ethyl-(2-methyl-allyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

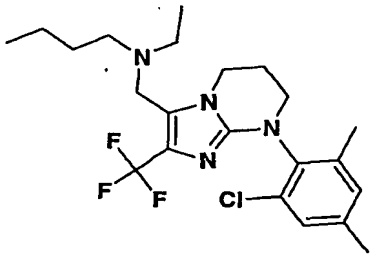
Example 107



Benzyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-methyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min. [M+H] 463.

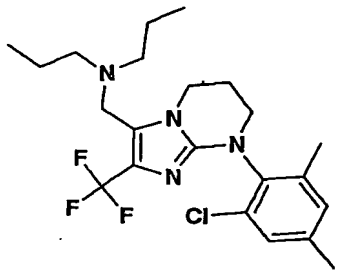
Example 108



Butyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-ethyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 443.

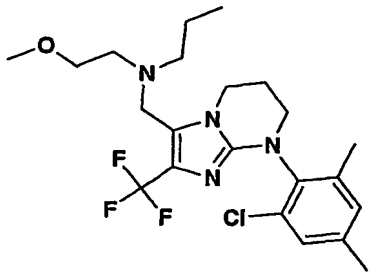
Example 109



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-dipropyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 443.

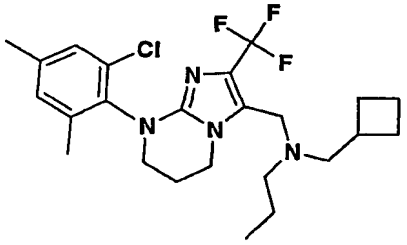
Example 110



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2-methoxy-ethyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 459.

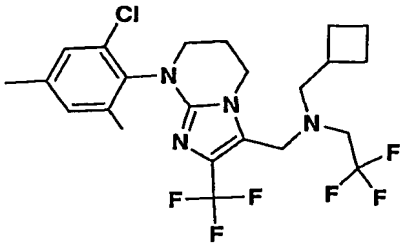
Example 111



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclobutylmethyl-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min. [M+H] 470.

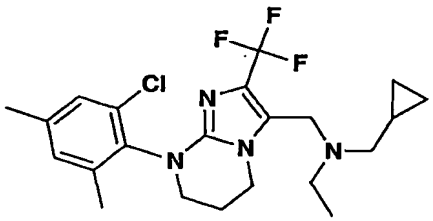
Example 112



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclobutylmethyl-(2,2,2-trifluoro-ethyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min. [M+H] 509.

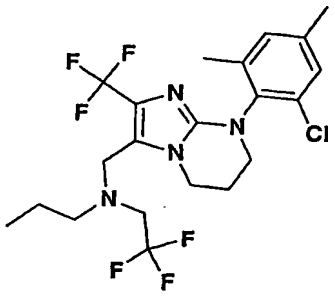
Example 113



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclopropylmethyl-ethyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

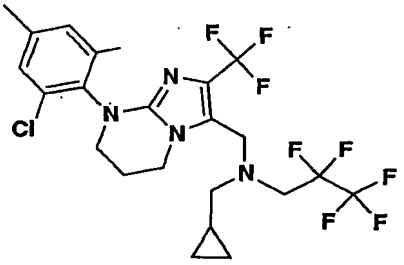
Example 114



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-propyl-(2,2,2-trifluoro-ethyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 483.

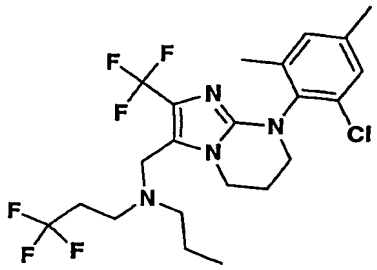
Example 115



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclopropylmethyl-(2,2,3,3,3-pentafluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min. [M+H] 545.

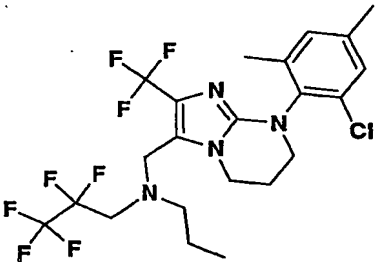
Example 116



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-propyl-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min. [M+H] 497.

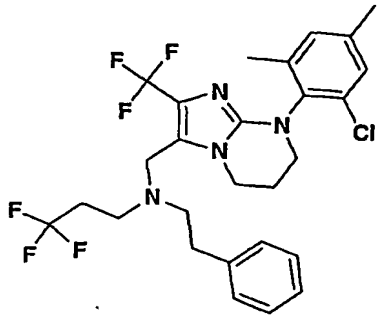
Example 117



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2,2,3,3,3-pentafluoro-propyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min. [M+H] 533.

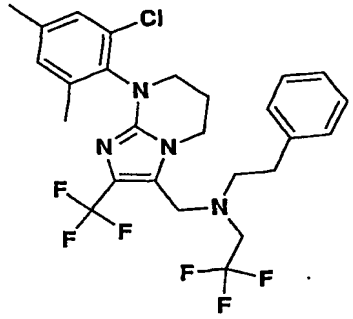
Example 118



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-phenethyl-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min. [M+H] 560.

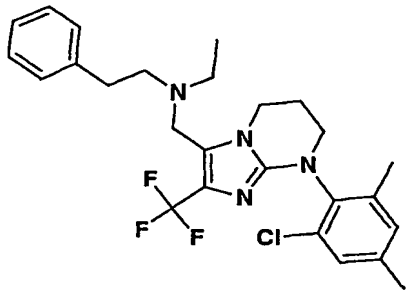
Example 119



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-phenethyl-(2,2,2-trifluoro-ethyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.9 min. [M+H] 545.

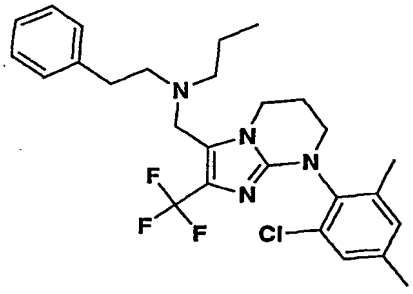
Example 120



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-ethyl-phenethyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min. [M+H] 491.

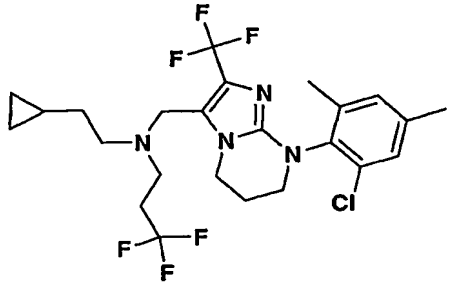
Example 121



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-phenethyl-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min. [M+H] 505.

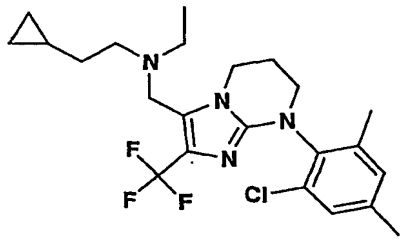
Example 122



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2-cyclopropyl-ethyl)-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 523.

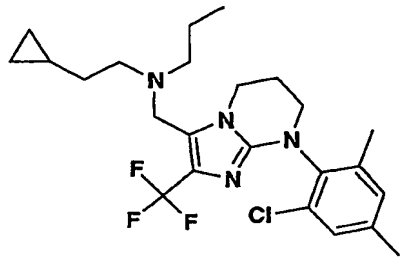
Example 123



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2-cyclopropyl-ethyl)-ethyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min. [M+H] 455.

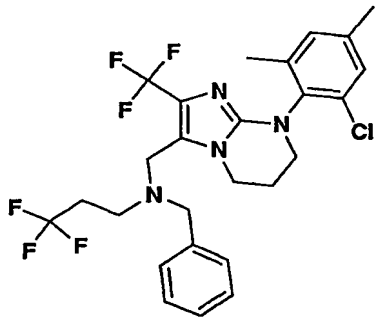
Example 124



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2-cyclopropyl-ethyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min. [M+H] 469.

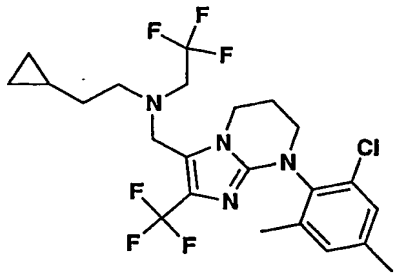
Example 125



Benzyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 545.

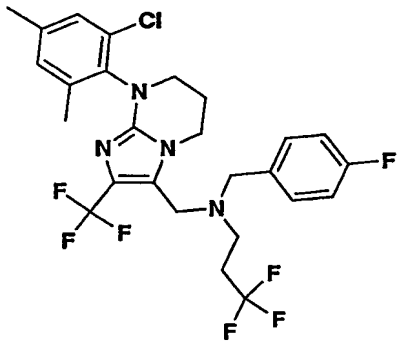
Example 126



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(2-cyclopropyl-ethyl)-(2,2,2-trifluoro-ethyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 509.

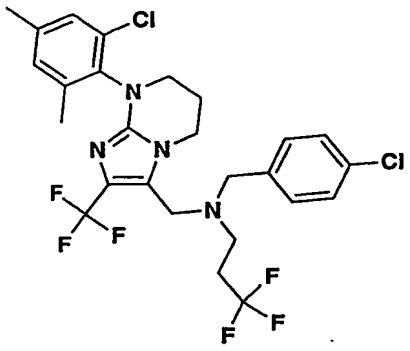
Example 127



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(4-fluoro-benzyl)-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 563.

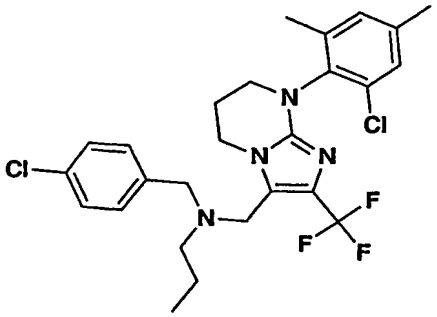
Example 128



(4-Chloro-benzyl)-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 580.

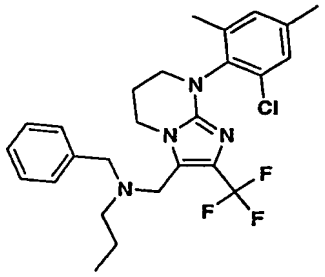
Example 129



(4-Chloro-benzyl)-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min. [M+H] 526.

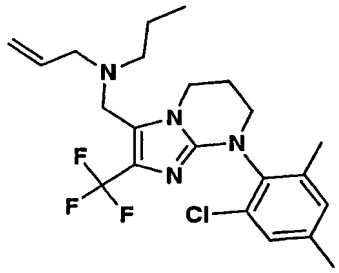
Example 130



Benzyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.5 min. [M+H] 491.

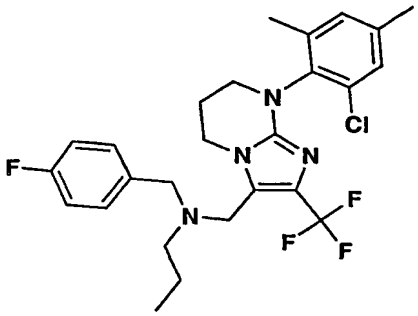
Example 131



Allyl-[8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 441.

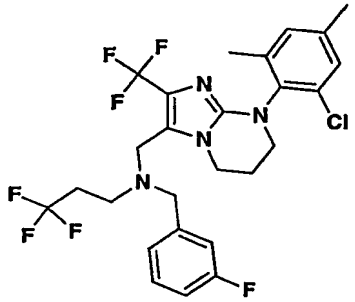
Example 132



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(4-fluoro-benzyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min. [M+H] 509.

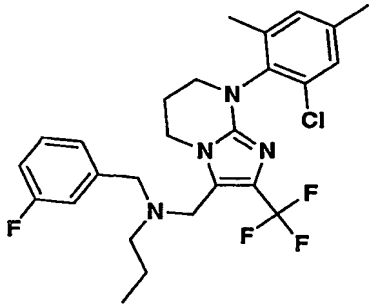
Example 133



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3-fluoro-benzyl)-(3,3,3-trifluoro-propyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 563.

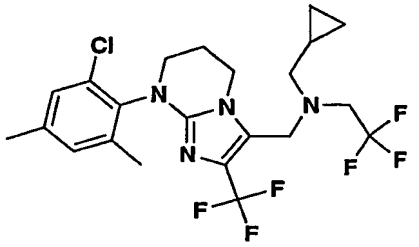
Example 134



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(3-fluoro-benzyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.6 min. [M+H] 509.

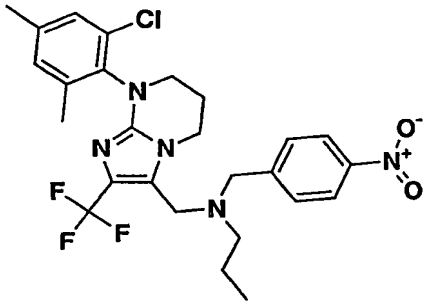
Example 135



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclopropylmethyl-(2,2,2-trifluoro ethyl)-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.8 min. [M+H] 495.

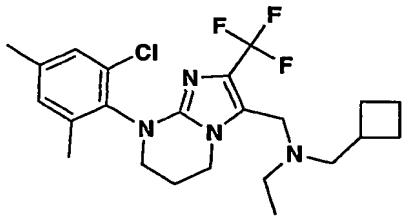
Example 136



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-(4-nitro-benzyl)-propyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.7 min. [M+H] 536.

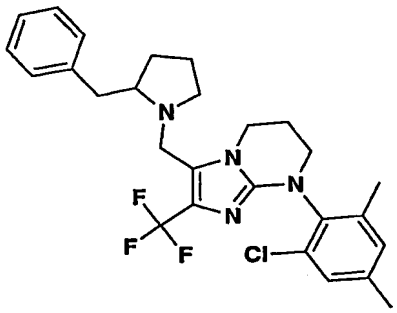
Example 137



[8-(2-Chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidin-3-ylmethyl]-cyclobutylmethyl-ethyl-amine, scheme 7: (KK)

Prepared as described for the example above. LC/MS: t_R = 1.4 min. [M+H] 455.

Example 138

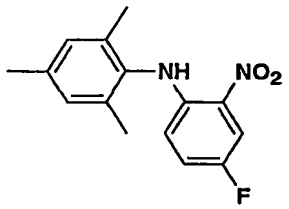


3-(2-Benzyl-pyrrolidin-1-ylmethyl)-8-(2-chloro-4,6-dimethyl-phenyl)-2-trifluoromethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrimidine, scheme 7: (KK)

LC/MS: t_R = 1.5 min. [M+H] 503.

The following **Intermediates 45-94** may be used to synthesize **Examples 139-282.**

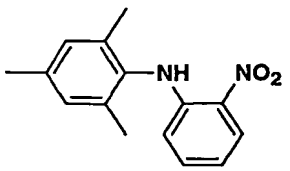
Intermediate 45



(4-Fluoro-2-nitro-phenyl)-(2,4,6-trimethyl-phenyl)-amine[1], scheme 1: (B)

A mixture of 2,4,6-trimethlaniline (42.1 mL, 300 mmol), 2,5-difluoro-nitrobenzene (16.3 mL, 150 mmol) and anhydrous potassium fluoride (10.5 g, 180 mmol) was heated and stirred at 180°C for 60 h. After cooling, the mixture was partitioned between dichloromethane (170 mL) and water (150 mL). The aqueous layer was extracted with dichloromethane (60 mL). The combined organic layers were washed with water and brine. Solvents were removed in vacuo and the residue purified by silica gel chromatography eluting with 40% dichloromethane/hexanes to afford the title compound as a red solid (36.92 g, 100% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.00 (s, 1H), 7.93 (dd, J = 9.1, 3.0 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.99 (s, 2H), 6.37 (dd, J = 9.4, 4.7 Hz, 1H), 2.33 (s, 3H), 2.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 151.4, 141.8, 137.6, 136.3, 132.6, 129.6, 124.9 (d, J = 23.8 Hz), 116.5 (d, J = 7.0 Hz), 111.75 (d, J = 26.2 Hz).

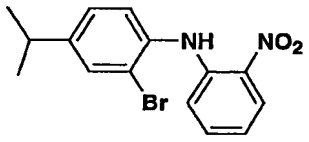
Intermediate 46



(2-Nitro-phenyl)-(2,4,6-trimethyl-phenyl)-amine:[3], scheme 1: (B)

Prepared as described for the example above. Chromatography using dichloromethane/hexanes (30%) as eluent and recrystallization from anhydrous ethanol afforded the title compound as orange needle crystals (15.4 g, 40% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.13 (br s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.00 (s, 2H), 6.70 (t, J = 7.2 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 2.35 (s, 3H), 2.16 (s, 6H).

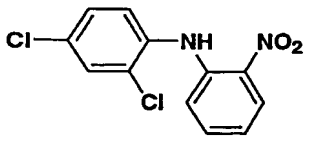
Intermediate 47



(2-Bromo-4-isopropyl-phenyl)-(2-nitro-phenyl)-amine, scheme 1: (B)

Prepared as described for the example above. Chromatography using dichloromethane/hexanes (20%) as eluent and vacuum distillation to remove unreacted 2-bromo-4-*iso*-propylaniline afforded the title compound as a red solid (12 g, 24% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.41 (br s, 1H), 8.21 (dd, J = 8.6, 1.6 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.20 (dd, J = 8.1, 2.0 Hz, 1H), 7.08 (dd, J = 8.6, 1.0 Hz, 1H), 6.81 (t, J = 7.0 Hz, 1H), 2.92 (septet, J = 7.0 Hz, 1H), 1.27 (d, J = 6.9 Hz, 6H).

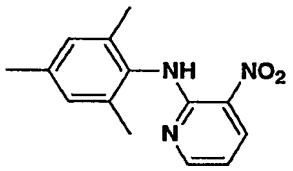
Intermediate 48



(2,4-Dichloro-phenyl)-(2-nitro-phenyl)-amine, scheme 1: (B)

Prepared as described for the example above. Chromatography using dichloromethane/hexanes (10% and 20%) as eluent and recrystallization from 95% ethanol afforded the title compound as red needle crystals (8.5 g, 20% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1H), 8.22 (dd, J = 8.5, 1.5 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.27 (dd, J = 8.6, 2.3 Hz, 1H), 7.13 (dd, J = 8.6, 1.0 Hz, 1H), 6.88 (td, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.0, 135.7, 135.1, 134.6, 130.5, 130.3, 129.3, 127.9, 126.8, 124.8, 118.9, 116.2.

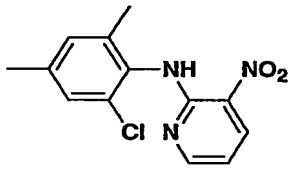
Intermediate 49



(3-Nitro-pyridin-2-yl)-(2,4,6-trimethyl-phenyl)-amine, scheme 1: (B)

A mixture of 2-chloro-3-nitro-pyridine (24.05 g, 152 mmol), 2,4,6-trimethylaniline (60 ml, 427 mmol), and Cs_2CO_3 (59.4 g, 182.4 mmol) was heated at 100 °C for 24 h. Flash chromatography using 1) methylene chloride /Hexanes (1:4) and 2) methylene chloride, followed by recrystallization from 95% ethanol. The title compound was obtained as an orange-yellow crystals (17.0 g, 44% yield). ^{1}H NMR ($CDCl_3$, 5 MHz) δ 9.38 (s, 1H), 8.51 (d, J = 5.8 Hz, 1H), 8.38 (s, 1H), 7.00 (s, 2H), 6.73 (s, 1H), 2.34 (s, 3H), 2.18(s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 152.1, 137.2, 135.7, 135.4, 132.3, 129.1, 128.3, 112.8, 21.1, 18.5.

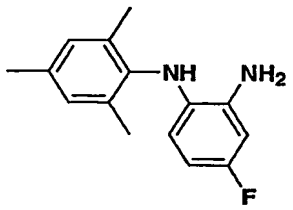
Intermediate 50



(2-Chloro-4,6-dimethylphenyl)-(3-nitro-pyridin-2-yl)-amine, scheme 1: (B)

A mixture of 2-chloro-3-nitro-pyridine (55.8 g, 352 mmol), 2-chloro-4,6-trimethylaniline (110 g, 704 mmol), and KF (28.6 g, 493 mmol) was heated at 190°C for 40 h. After cooling to room temperature, the mixture was extracted with methylene chloride and 1N NaOH. The combined organic layers were washed with water and brine, then dried over $MgSO_4$. Solvents were removed in vacuo, and the residue was subjected to vacuum distillation to remove unreacted 2-chloro-4,6-trimethylaniline. The resulting brownish solid was subjected to flash chromatography using 1) methylene chloride /hexanes (1:1) and 2) methylene chloride, followed by recrystallization from 95% ethanol. The title compound was obtained as yellow crystals (9.8 g, 10% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.39 (br s, 1H), 8.51 (dd, J = 8.3, 1.8 Hz, 1H), 8.37 (dd, J = 4.5, 1.7 Hz, 1H), 7.18 (s, 1H), 7.04 (s, 1H), 6.78 (dd, J = 8.3, 4.5 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H).

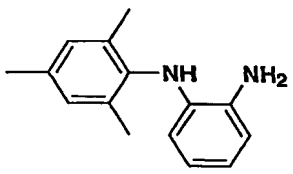
Intermediate 51



4-Fluoro-N^1-(2,4,6-trimethyl-phenyl)-benzene-1,2-diamine, scheme 1: (C)

Palladium on carbon (10%) (0.54 g) was added to a solution of (4-fluoro-2-nitro-phenyl)-(2,4,6-trimethyl-phenyl)-amine (5.32 g, 19.4 mmol) in ethyl acetate (40 mL) under nitrogen at room temperature in a 500 mL round-bottomed flask. The flask was evacuated under high vacuum (<2 mm Hg) and purged with hydrogen six times at room temperature, then it was attached to a balloon filled with hydrogen. After the reaction mixture was stirred at room temperature for 4.0 h under 1 atmosphere of hydrogen, the balloon was removed and a stream of nitrogen was bubbled through the reaction mixture for 10 min. The reaction mixture was filtered through a pad of celite and solvents were removed in vacuo to afford the title compound as a red solid (4.74 g, 100% yield). The purity of this compound was determined to be 98% by LC/MS. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (s, 2H), 6.52 (dd, J = 9.8, 2.7 Hz, 1H), 6.32 (td, J = 8.6, 2.7 HZ, 1H), 6.22 (dd, J = 8.7, 5.7 Hz, 1H), 2.32 (s, 3H), 2.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 156.7, 138.2 (d, J = 10.5 Hz), 137.6, 133.5, 132.3, 129.5, 117.3 (d, J = 9.5 Hz), 105.1 (d, J = 22 Hz), 102.9 (d, J = 25.5 Hz),20.8, 18.0; Mass spec.: 245.14 (MH^+)

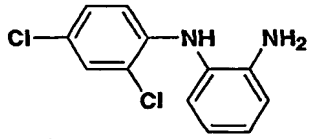
Intermediate 52



N-(2,4,6-Trimethyl-phenyl)-benzene-1,2-diamine, scheme 1: (C)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (s, 2H), 6.88 (d, J = 7.5 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.25 (d, J = 7.2 Hz, 1H), 4.95 (br s, 2H), 2.31 (s, 3H), 2.13 (s, 6H); Mass spec.: 227.15 (MH^+)

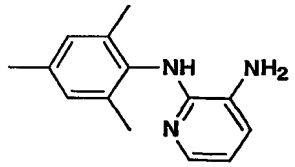
Intermediate 53



N-(2,4-Dichloro-phenyl)-benzene-1,2-diamine, scheme 1: (C)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 – 7.00 (m, 4H), 6.89 – 6.79 (m, 2H), 6.52 (d, J = 8.8 Hz, 1H), 5.74 (s, 1H), 4.27 (br s, 2H); Mass spec.: 253.12 (MH^+)

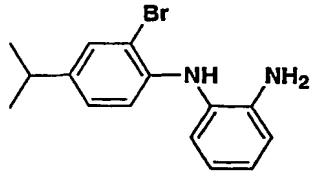
Intermediate 54



N^2-(2,4,6-Trimethyl-phenyl)-pyridine-2,3-diamine, scheme 1: (C)

Prepared as described for the example above. Mass spec.: 228.16 (MH^+)

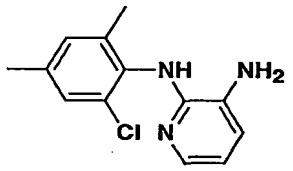
Intermediate 55



N-(2-Bromo-4-isopropyl-phenyl)-benzene-1,2-diamine[2], scheme 1: (C)

To a solution of (2-bromo-4-isopropyl-phenyl)-(2-nitro-phenyl)-amine (8.2 g, 24.5 mmol) in tetrahydrofuran (35 mL) and water (35 mL) at room temperature, was added NH_4OH (33.6 mL) and $Na_2S_2O_4$ (21.3 g, 122.5 mmol. After stirring at room temperature for 5 h, water (70 mL) was added and the mixture was extracted with ethyl acetate (175 mL). After separation, the aqueous layer was saturated with NaCl, and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with sat. $NaHCO_3$, water, brine, and dried over Na_2SO_4. Solvents were removed in vacuo to afford the title compound a red viscous liquid (5.3 g, 71% yeld). The purity of this compound was determined to be 95% by LC/MS and it was used for the next step without further purification. Mass spec.: 307.08 (MH^+).

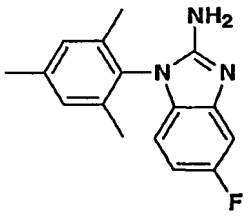
Intermediate 56



N^2-(2-Chloro-4,6-dimethyl-phenyl)-pyridine-2,3-diamine, scheme 1: (C)

Prepared as described for the example above. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (dd, J = 5.0, 1.5 Hz, 1H), 7.11 (s, 1H), 6.97 (dd, J = 7.5, 1.6 Hz, 1H), 6.96 (s, 1H), 6.67 (dd, J = 7.5, 5.0 Hz, 1H), 5.89 (br s, 1H), 3.53 (br s, 2H), 2.29 (s, 3H), 2.13 (s, 3H); Mass spec.: 228.16 (MH^+)

Intermediate 57

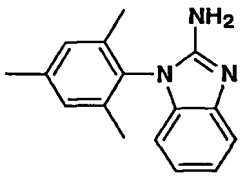


5-Fluoro-1-(2,4,6-trimethyl-phenyl)-1*H*-benzoimidazol-2-ylamine:[3], **scheme 1:**

(D)

A solution of cyanogen bromide (2.67 g, 25.2 mmol) in anhydrous ethanol (10 mL) was added at 0°C to a solution of 4-fluoro-N^1-(2,4,6-trimethyl-phenyl)-benzene-1,2-diamine (4.74 g, 19.4 mmol) in anhydrous ethanol (20 mL) under nitrogen. The reaction mixture was warmed up to room temperature for 10 min, then was heated at 155°C for 40 min with a flow of nitrogen to remove ethanol. Upon cooling to room temperature, the resulting solids were transferred to a separatory funnel via dichloromethane (70 mL), and washed sequentially with 1 N sodium hydroxide (2 × 35 mL), water and brine. The organic layer was dried over anhydrous sodium sulfate and solvents were removed in vacuo to afford the title compound as a red solid (5.11 g, 98% yield). The purity of this compound was determined to be 95% by LC/MS. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (dd, J = 9.7, 2.4 Hz, 1H), 7.06 (s, 2H), 6.69 (td, J = 9.1, 2.4 Hz, 1H), 6.56 (dd, J = 8.5, 4.7 Hz, 1H), 2.38 (s, 3H), 1.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0, 157.9, 154.2, 143.3, 139.9, 137.4, 129.8, 128.8, 107.8 (d, J = 10.2 Hz), 106.9 (d, J = 25.3 Hz), 103.1 (d, J = 25.2 Hz)21.1, 17.5; Mass spec.: 270.17 (MH^+).

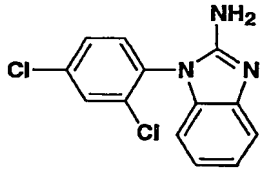
Intermediate 58



1-(2,4,6-Trimethyl-phenyl)-1*H*-benzoimidazol-2-ylamine, scheme 1: (D)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, J = 8.1 Hz, 1H), 7.16 (td, J = 7.6, 1.2 Hz, 1H), 7.06 (s, 2H), 7.01 (td, J = 7.2, 0.6 Hz, 1H), 6.71 (dd, J = 7.8, 0.6 Hz, 1H), 2.38 (s, 3H), 1.98 (s, 6H); Mass spec.: 252.09 (MH^+)

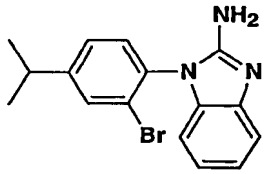
Intermediate 59



1-(2,4-Dichloro-phenyl)-1*H*-benzoimidazol-2-ylamine, scheme 1: (D)

Prepared as described for the example above. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 1.5 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.23 – 7.16 (m, 2H), 7.04 (t, J = 7.7 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H); Mass spec.: 278.08 (MH^+)

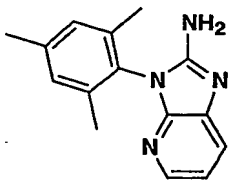
Intermediate 60



1-(2-Bromo-4-isopropyl-phenyl)-1*H*-benzoimidazol-2-ylamine, scheme 1: (D)

Prepared as described for the example above. Mass spec.: 330.08 (MH^+)

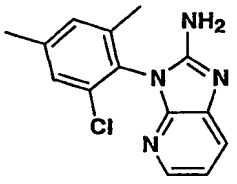
Intermediate 61



3-(2,4,6-Trimethyl-phenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-ylamine, scheme 1: (D)

To a mixture of N^2-(2,4,6-Trimethyl-phenyl)-pyridine-2,3-diamine (3.05 g, 13.4 mmol), $NaHCO_3$ (2.03 g, 24.1 mmol) in ethanol (40 mL) at 0°C, was added a solution of BrCN (2.55 g, 24.1 mmol) in ethanol (6 mL). The resulting mixture was stirred at 0°C for 1 h, room temperature for 8 h, and then 80°C for 8 h. Ethanol was removed in vacuo and the residue was taken up into a separatory funnel with methylene chloride (100 mL). The mixture was washed sequentially with 1N NaOH, water and brine, then the organic layer was dried over Na_2SO_4. After removing solvents, a brown solid was obtained. By LC-MS, the solid was a mixture of the desired product and the unreacted starting material in a ratio of 4:1 in favor of the desired product. Mass spec.: 253.17 (MH^+).

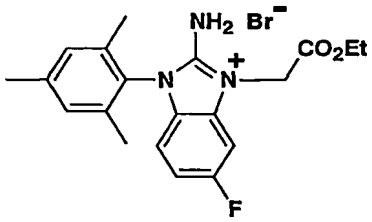
Intermediate 62



3-(2-Chloro-4,6-dimethyl-phenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-ylamine, scheme 1: (D)

Prepared as described for the example above. Mass spec.273.20 (MH^+)

Intermediate 63



3-Ethoxycarbonylmethyl-1-(2,4,6-trimethylphenyl)-2-amino-5-fluoro-benimidazolium bromide:[4], scheme 1: (E)

Ethyl bromoacetate (2.3 mL, 20.9 mmol) was added at room temperature to a solution of 5-fluoro-1-(2,4,6-trimethyl-phenyl)-1*H*-benzoimidazol-2-ylamine (5.11 g, 19.0 mmol) in acetone (100 mL). The resulting mixture was heated at reflux for 14 h. Upon cooling to room temperature, acetone was removed in vacuo. Solids were transferred onto a filtering funnel and washed with ether (2×15 mL) to afford the title compound as a pink solid (7.42 g, 90%). The solids were used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 2H), 7.11 (s, 2H), 7.11 – 6.96 (m, 2H), 6.78 (dd, J = 8.6, 4.1 Hz, 1H), 5.69 (s, 2H), 4.28 (qd, J = 7.1, 1.0 Hz, 2H), 2.38 (s, 3H), 2.02 (s, 6H), 1.32 (td,J = 7.1, 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 162.0, 158.7, 151.1, 142.3, 136.9, 130.7, 126.2, 124.7, 112.4 (d, J = 25.0 Hz), 111.2 (d, J = 9.4 Hz), 98.7 (d, J = 29.2 Hz), 63.0, 46.8, 21.3, 17.4, 14.1.